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(54) Title: PHOSPHORUS-CONTAINING MACROCYCLES

(57) Abstract: This invention concerns a new family of phosphorus-containing macrocycles containing various phosphonate- and phosphonate-containing moieties.



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Phosphorus-Containing Macrocycles

Background of the Invention

Cancers of the bone, both primary bone cancers and those that have metastasized to bone (bone metastases), involve complex molecular processes and have been difficult to treat. Bone metastases, a frequent consequence of common malignancies such as breast, lung and prostate cancer, are often associated with severe bone pain and pathological fractures due to increased bone fragility. Primary bone cancers (e.g., osteogenic sarcoma) present treatment challenges, and patients often require limb amputation and/or radiation therapy. In the bone microenvironment, as it is currently understood, metastasized cancer cells produce activating factors (e.g., PTHrP) that stimulate osteoclast-mediated bone resorption. Bone-derived growth factors (e.g., TGF- β and IGF1) are subsequently released, promoting cancer-cell proliferation and the amplification of a cycle that produces net osteolytic (bone destructive) consequences.

The development of new therapeutic agents for treating cancers of the bone, preferably agents that act directly and potently to inhibit bone breakdown and tumor growth would be highly desirable.

Rapamycin is a macrolide antibiotic produced by *Streptomyces hygroscopicus*. It binds to a FK506-binding protein, FKBP12, with high affinity to form a rapamycin:FKBP complex. Reported K_d values for that interaction are as low as 200 pM. The rapamycin:FKBP complex binds with high affinity to the large cellular protein, FRAP, to form a tripartite, [FKBP:rapamycin]:[FRAP], complex. In that complex rapamycin can be viewed as a dimerizer or adapter to join FKBP to FRAP. Formation of the complex is associated with rapamycin's various biological activities.

Rapamycin is a potent immunosuppressive agent and is used clinically to prevent rejection of transplanted organs. Rapamycin and/or its analogs, AP23573 (ARIAD), CCI 779 (Wyeth) and SDZ Rad ("RAD001", Novartis) are promising agents for treating certain cancers, for immune suppression and/or for helping to decrease the incidence of restenosis following interventional cardiology. Rapamycin has also been shown to have activity as an antifungal agent, in the experimental allergic encephalomyelitis model (a model for multiple sclerosis), in the adjuvant arthritis model (for rheumatoid arthritis), in inhibiting the formation of IgE-like antibodies, and for treating or preventing lupus erythematosus, pulmonary inflammation, insulin dependent diabetes mellitus, adult T-cell leukemia/lymphoma, and smooth muscle cell proliferation and intimal thickening following vascular injury. See e.g. published US Patent application 2001/0010920.

Rapamycin's potential for providing relief from such an important swath of cruel diseases has stimulated the search for rapamycin analogs with improved therapeutic index, pharmacokinetics, ease or economy of production or formulation, etc. The resulting investigation by industrial and academic researchers has led to the exploration of materials

5 and methods for effecting chemical transformations of rapamycin, including reductions of ketones, demethylations, epimerizations, various acylations and alkylations of hydroxyls, etc.

A large number of structural variants of rapamycin have now been reported, typically arising as alternative fermentation products and/or from synthetic efforts. For example, the extensive literature on analogs, homologs, derivatives and other compounds related
10 structurally to rapamycin ("rapalogs") include, among others, variants of rapamycin having one or more of the following modifications relative to rapamycin: demethylation, elimination or replacement of the methoxy at C7, C42 and/or C29; elimination, derivatization or
15 replacement of the hydroxy at C13, C43 and/or C28; reduction, elimination or derivatization of the ketone at C14, C24 and/or C30; replacement of the 6-membered piperolate ring with a 5-membered prolyl ring; and alternative substitution on the cyclohexyl ring or replacement
20 of the cyclohexyl ring with a substituted cyclopentyl ring. Additional historical information is presented in the background sections of US Patent Nos. 5,525,610; 5,310,903 and 5,362,718. See also US Patent No. 5,527,907. Materials and methods have even been developed for the remarkably effective and selective epimerization of the C-28 hydroxyl
25 group (WO 01/14387). See also USSN 10/357,152 and PCT/US03/03030 for additional background on methods and materials for the preparation and use of rapamycin analogs containing various phosphorus-containing moieties.

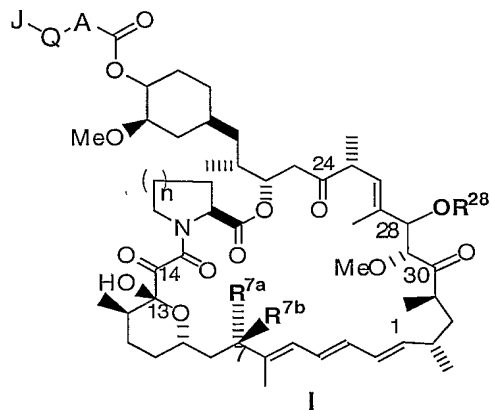
New rapalogs with attractive physicochemical or functional characteristics relative to rapamycin, e.g., in therapeutic index, bioavailability, pharmacokinetics, stability, tissue
25 distribution, etc., would also be of interest for a variety of pharmaceutical uses including among others bone cancers and other bone disorders involving bone resorption.

The three rapalogs currently in clinical development as anti-cancer agents include two with conventional structural modifications, i.e., acylation or alkylation of the oxygen atom at C-43 [CCI 779 and SDZ RAD, respectively; see e.g., Yu, K. et al., Endocrine Related
30 Cancer (2001) 8, 249-258; Georger, B. et al., Cancer Res. (2001) 61 1527-1532] and Dancey, Hematol Oncol Clin N Am 16 (2002):1101 – 1114] and one with a rather unusual phosphine oxide substituent at that site (AP23573).

The invention described below represents a rather dramatic departure in the design of new rapalogs based on the incorporation of more elaborate phosphorus-containing
35 moieties.

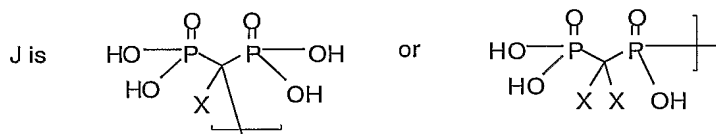
5 **Summary of the Invention**

This invention provides a new family of compounds of Formula (I):



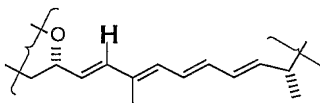
and pharmaceutically acceptable derivatives thereof. Compositions containing such compounds and uses thereof are also provided.

10 In the compounds of this invention, each occurrence of **A** is independently -O-, -S- or -NR²-; each occurrence of **Q** is independently an aliphatic, heteroaliphatic, aryl or heteroaryl moiety, linking A to J;



each occurrence of **X** is independently H, -OR or halo;

one of **R^{7a}** and **R^{7b}** is H and the other is H, halo, -R^A, -OR^A, -SR^A, -OC(O)R^A, -OC(O)NR^AR^B, -NR^AR^B, -NR^BC(O)R^A, -NR^BC(O)OR^A, -NR^BSO₂R^A or -NR^BSO₂NR^AR^B; or **R^{7a}** and **R^{7b}**, taken together, are H in the tetraene moiety:

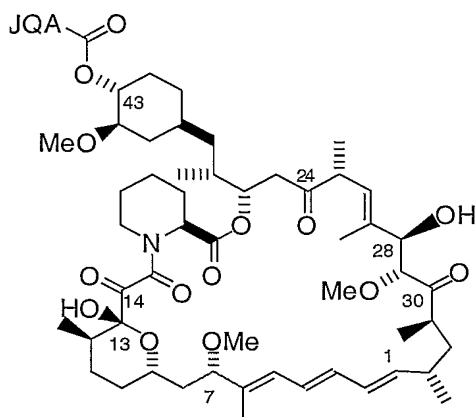


R^A is R², **R^B** is OH or R² and each occurrence of R² is independently H or an aliphatic, heteroaliphatic, aryl, or heteroaryl moiety (in some cases one or both of R^A and R^B is H); **R²⁸** is hydrogen or COAQJ; and **n** is 1 or 2; wherein each of the foregoing aliphatic and heteroaliphatic moieties is independently branched or unbranched, cyclic or acyclic, and substituted or unsubstituted, and each aryl or heteroaryl moiety is independently substituted or unsubstituted.



25

This new family includes a number of classes of compounds of particular interest, including compounds of the following structure in which J, Q and A are as previously defined:

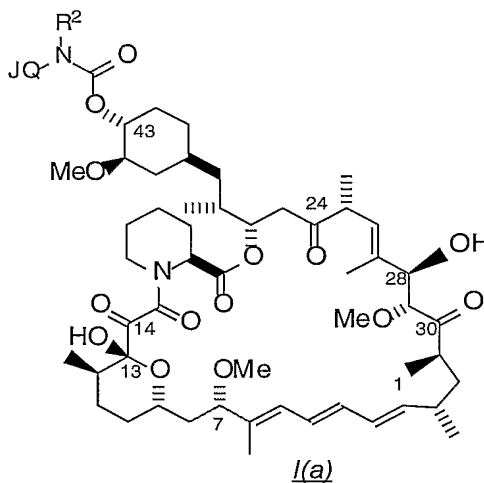


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In other classes of compounds of this invention, compounds have one or more additional structural modifications relative to rapamycin, modifications involving altered stereochemistry at one or more sites including C43 and C28, modification in the substituent or stereochemistry at C7, reduction of one or more of the ketone functionalities, demethylation at one or more sites, substitution on the hydroxyl group at C28, etc.

10

Of particular interest are family members of Formula I in which A is $-NR^2-$, including the subset of such carbamates shown in Figure I(a):



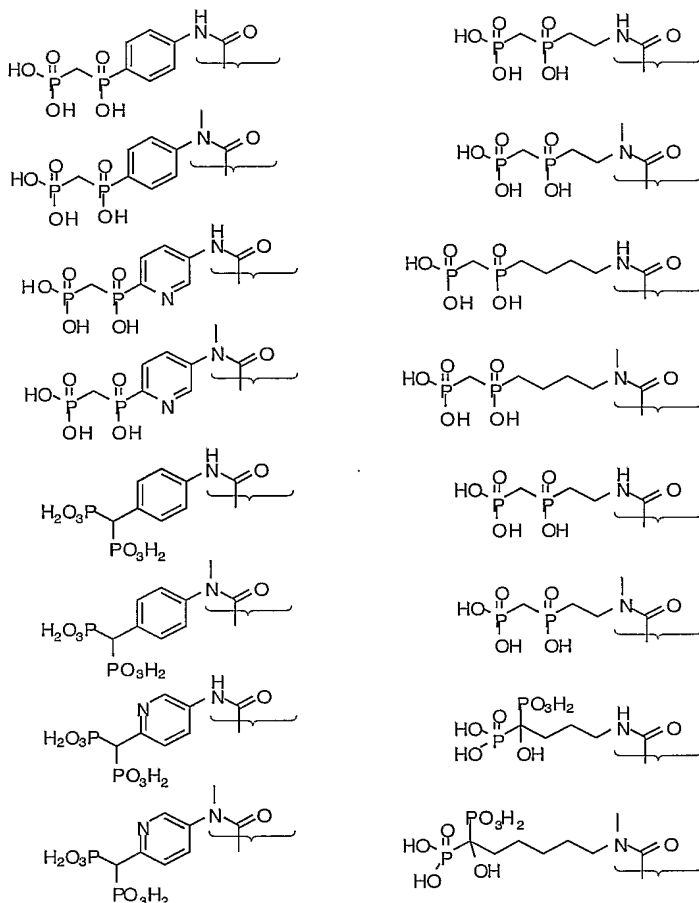
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Exemplary carbamates of Formula I(a) contain $JQN(R^2)CO-$ groups such as are illustrated in the table which follows and in the Examples further below.

5

Table of Illustrative Carbamates of Formula I(a)

Where $\text{JQNR}^2\text{-CO-}$ is selected from the following:

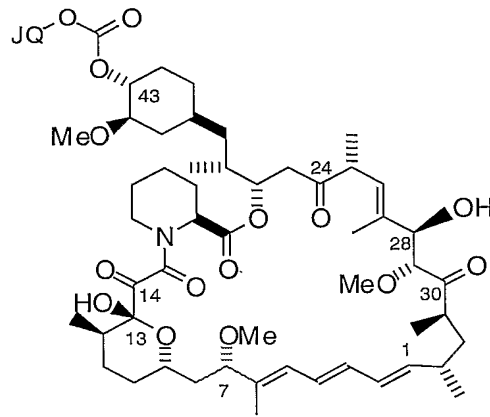


10

These charts are intended to be illustrative rather than comprehensive. Thus, carbamates of this invention may for example contain R^2 groups other than H or Me (e.g., may contain other alkyl groups, aryl groups, arylalkyl groups, etc.) and may contain aliphatic Q groups of other lengths, e.g. C2 to C8, preferably C2 to C5. Furthermore, and as detailed elsewhere, in some embodiments, carbamates of this invention contain one or more additional modifications (relative to rapamycin) at positions other than C43.

20

Also of particular interest are family members of Formula I in which A is $-\text{O}-$, as illustrated by compounds defined in Formula I(b):



5

I(b)

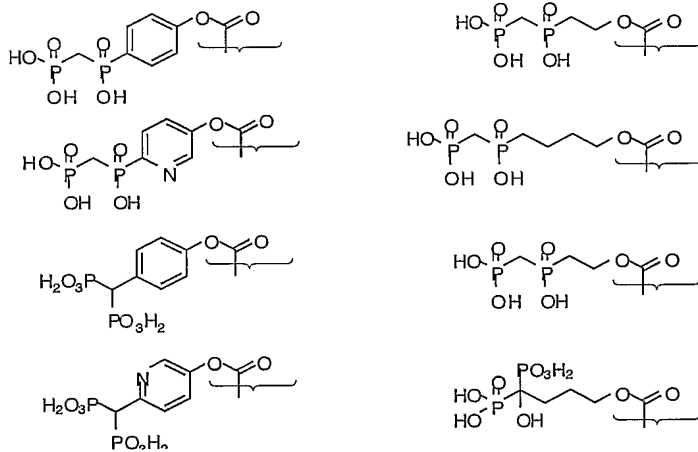
Illustrative carbonates of Formula I(b) contain JQOCO- groups such as are illustrated in the table which follows and in the Examples further below.

10

Table of Illustrative Carbonates of Formula I(b):

Where JQA-O-CO- is selected from the following:

15



20

Note: Again, such carbonates may for example contain aliphatic Q groups of other lengths, e.g. C2 to C8, preferably C2 to C5, and in some embodiments, carbonates of this invention contain one or more additional modifications (relative to rapamycin) at positions other than C43.

5 Also of particular interest are family members of Formula I in which Q is aliphatic, whether A is O, NR² or S, although carbamates and carbonates are of special interest. Such aliphatic groups preferably contain 1 – 8 contiguous aliphatic carbon atoms, and typically 2 – 8 carbon atoms. Such compounds include among others those in which Q is a 2 – 4 carbon alkyl group. These family members include, among others, compounds of Formulas I(a) and
10 I(b) in which Q is aliphatic, preferably C1 – C8 and are illustrated in the various compounds depicted above and in the Examples further below.

 Also of particular interest are family members of Formula I in which Q is aryl or heteroaryl, whether A is O, NR² or S. Such compounds in which Q is a substituted phenyl or pyridyl group are illustrated in the Examples which follow. These family members include
15 among others compounds of Formulas I(a) and I(b) in which Q is aryl or heteroaryl. Again, carbamates and carbonates are of special interest. Again, these family members are illustrated in the various compounds depicted above and in the Examples further below.

 Additional classes of particular interest are noted below:

20

(a) Compounds as above, but with one or more additional structural modifications relative to rapamycin. Numerous such modifications are known in the art and are alluded to elsewhere herein, including replacement of the –OMe substituent at C7, or alteration of its stereochemistry; epimerization at one or both of C28 and C43; reduction of one or more of
25 the ketone functionalities e.g. at one or both of ring positions 24 and 30; desmethylation at one or more sites; reduction of one or more of the double bonds between C1 and C6; and/or use of the prolyl analog instead of the pipicolate structure of rapamycin. Compounds of this invention may be prepared by starting with the appropriate rapamycin analog in place of rapamycin itself.

30

(b) Compounds of the invention with a molecular below 1700, preferably below 1500, and more preferably below 1300 mass units (not counting the contribution of a counter ion in cases in which the compound is in a salt form or of a labile pro-drug moiety in the case of a pro-drug).

35

(c) Compounds of the invention which are chemically linked to a polyethylene glycol moiety or other solubility-enhancing group. Examples include glycinate (or other aminocarboxylate) esters or PEGylated esters (see e.g. WO 02/24706) of any free –OH moiety of a rapalog of this invention.

40

(d) Compounds of the invention that retain at least 0.01, preferably 0.1 and more preferably at least 0.5 times the potency of rapamycin in a T cell proliferation assay.

5 (e) Compounds in which one or more hydroxyl groups of one or more
phosphonate and/or phosphinate groups is replaced with –OR, where each such R group is
independently chosen from methyl, ethyl, n-propyl, –propyl, n-butyl, 2-butyl, t-butyl, phenyl,
or heteroaryl, each of which optionally bearing one or more halo, –OH, alkoxy–,
10 alkoxyalkoxy–, haloalkyl–, hydroxyalkoxy–, acyl–, acyloxy–, heterocyclic, aryl or heteroaryl
substituents.

(f) Compounds in which X is OH, or, in cases containing geminal X groups, one
is OH and the other is H.

15 (g) Compounds in which X is OR, or, in cases containing geminal X groups, one
is OR and the other is H, where each such R group is independently chosen from methyl,
ethyl, n-propyl, –propyl, n-butyl, 2-butyl, t-butyl, phenyl, or heteroaryl, each of which
optionally bearing one or more halo, –OH, alkoxy–, alkoxyalkoxy–, haloalkyl–,
20 hydroxyalkoxy–, acyl–, acyloxy–, heterocyclic, aryl or heteroaryl substituents

20

Some other aspects of the invention include:

–A composition comprising a compound of the invention, including any of the various types
of compounds noted above, together with a pharmaceutically acceptable vehicle and
25 optionally containing one or more pharmaceutically acceptable excipients. The composition
may be one which is suitable for oral or parenteral administration to a subject, e.g. a
mammalian subject, including a human patient. Compositions may be prepared using
conventional materials such that they are suitable for administration by any of the routes of
administration noted in this document.

30

–The use of the compounds of this invention to prepare compositions useful for the various
medical and other uses noted herein.

35 –A method for treating osteoporosis or another bone disease involving bone resorption,
graft vs. host disease, lupus, rheumatoid arthritis, diabetes mellitus, myasthenia gravis,
multiple sclerosis, psoriasis, dermatitis, eczema, seborrhea, inflammatory bowel disease,
pulmonary inflammation, ocular uveitis; adult T-cell leukemia/lymphoma; fungal infections;
hyperproliferative restenosis; graft vascular atherosclerosis; cerebral vascular disease,
coronary artery disease, cerebrovascular disease, arteriosclerosis, atherosclerosis,
40 nonatheromatous arteriosclerosis, or vascular wall damage from cellular events leading
toward immune mediated vascular damage, stroke or multiinfarct dementia in a subject in
need thereof, by administering to such a subject a therapeutically effective amount of a
composition containing a compound of the invention.

5 –A method for treating cancer, especially a bone cancer, in a subject in need thereof, which
comprises administering to the subject a treatment effective amount of a composition
containing a compound of this invention. Various cancers which may be thus treated are
noted elsewhere herein. This treatment may be provided in combination with one or more
10 or more of an anti-cancer alkylating or intercalating agent (e.g. an anthracycline such as
doxorubicin, doxil, etc.); an antiestrogen; a taxane; an inhibitor of a kinase (e.g., an inhibitor
of Src, BRC/Abl, kdr, aurora-2, glycogen synthase kinase 3 (“GSK-3”), cKit); an antibody to a
receptor or hormone implicated in a cancer (e.g. EGFR, PDGFR, IGF-R and IL-2); or a
soluble receptor or other receptor antagonist to such receptor; a proteasome inhibitor or
15 other NF-kB inhibitor; another mTOR inhibitor [e.g., AP23573 (see e.g. WO 03/064383, esp.
Example 9), rapamycin, CCI779, Everolimus, etc.]; or radiation. Examples of other
therapeutic agents are noted elsewhere herein and include among others, Zylprim,
alemtuzmab, altretamine, amifostine, nastrozole, antibodies against prostate-specific
membrane antigen (such as MLN-591, MLN591RL and MLN2704), arsenic trioxide, Avastin
20 ® (or other anti-VEGF antibody), bexarotene, bleomycin, busulfan, capecitabine, carboplatin,
Gliadel Wafer, celecoxib, chlorambucil, cisplatin (or other platinum-based anti-cancer agent),
cisplatin-epinephrine gel, cladribine, cytarabine liposomal, daunorubicin liposomal,
daunorubicin, daunomycin, dexrazoxane, docetaxel, doxorubicin, Elliott's B Solution,
epirubicin, estramustine, etoposide phosphate, etoposide, exemestane, fludarabine, 5-FU,
25 fulvestrant, gemcitabine, gemtuzumab-ozogamicin, goserelin acetate, hydroxyurea,
idarubicin, idarubicin, Idamycin, ifosfamide, imatinib mesylate, irinotecan (or other
topoisomerase inhibitor, including antibodies such as MLN576 (XR11576)), letrozole,
leucovorin, leucovorin levamisole, liposomal daunorubicin, melphalan, L-PAM, mesna,
methotrexate, methoxsalen, mitomycin C, mitoxantrone, MLN518 or MLN608 (or other
30 inhibitors of the flt-3 receptor tyrosine kinase, PDFG-R or c-kit), itoxantrone, paclitaxel,
Pegademase, pentostatin, porfimer sodium, Rituximab (RITUXAN®), talc, tamoxifen,
temozolamide, teniposide, VM-26, topotecan, toremifene, Trastuzumab (Herceptin®, or
other anti-Her2 antibody), 2C4 (or other antibody which interferes with HER2-mediated
signaling), tretinoin, ATRA, valrubicin, vinorelbine, or pamidronate, zoledronate or another
35 bisphosphonate.



40 This invention thus provides a new family of unusual rapalogs. These compounds,
rapamycin analogs modified relative to rapamycin at position 43, and optionally at C28, may
also be further derivatized relative to rapamycin, e.g. at one or more of C7, C28, C13, C24
and C30 and elsewhere, by adapting chemical transformations or otherwise incorporating
structural alterations such as those disclosed in US 6,258,823, WO 96/41865, WO

5 98/02441, WO 99/36553 and WO 01/14387 and in the other patent documents and scientific references cited therein or within this document. Compounds of interest include among others, those which bind to human FKBP12, or inhibit its rotamase activity, within two, and more preferably within one order of magnitude of results obtained with rapamycin in any conventional FKBP binding or rotamase assay.

10 Also included are pharmaceutically acceptable derivatives of the foregoing compounds, where the phrase "pharmaceutically acceptable derivative" denotes any pharmaceutically acceptable salt, ester, carbamate, or salt of such ester or carbamate of such compound, or any other adduct or derivative which, upon administration to a patient, is capable of providing (directly or indirectly) a JQA-containing rapalog as described herein, or
15 a biologically active metabolite or residue thereof. Pharmaceutically acceptable derivatives thus include among others pro-drugs of the rapalogs. A pro-drug is a derivative of a compound, usually with significantly reduced pharmacological activity, which contains an additional moiety which is susceptible to removal *in vivo* yielding the parent molecule as the pharmacologically active species. An example of a pro-drug is an ester which is cleaved *in*
20 *vivo* to yield a compound of interest. Various pro-drugs of rapamycin and of other compounds, and materials and methods for derivatizing the parent compounds to create the pro-drugs, are known and may be adapted to the present invention.

Compounds of this invention may be provided in substantially pure form (relative to side products, residual reactants and other unwanted materials), e.g., at least 50% pure,
25 suitably at least 60% pure, advantageously at least 75% pure, preferably at least 85% pure, more preferably at least 95% pure, especially at least 98% pure, all percentages being calculated on a weight/weight basis. An impure or less pure form of the compound may be useful in the preparation of a more pure form of the same compound or of a related compound (for example a corresponding derivative) suitable for pharmaceutical use.

30 Compounds of this invention having antifungal activity, including among others those with one or more phosphonate and/or phosphonate hydroxyl groups derivatized, and including among others those having a replacement C7 substituent in place of methoxyl, may be used as monotherapies or in combination with other antifungal agents to combat fungal infections in animals, especially mammals, including humans, in particular humans and
35 domesticated animals (including farm animals). The compounds may be used, for example, in the treatment of topical fungal infections caused by, among other organisms, species of *Candida* (e.g. *C. albicans*), *Trichophyton* (e.g. *Trichophyton mentagrophytes*), *Microsporum* (e.g. *Microsporum gypseum*) or *Epidermophyton* or in mucosal infections caused by *Candida albicans* (e.g. thrush and vaginal candidiasis). They may also be used in the treatment of
40 systemic fungal infections caused by, for example *Candida albicans*, *Cryptococcus neoformans*, *Aspergillus fumigatus*, *Coccidioides*, *Paracoccidioides*, *Histoplasma* or *Blastomyces* spp. They may also be of use in treating eumycotic mycetoma, chromoblastomycosis and phycosmycosis. Other fungal infections for which compounds of this invention are applicable and considerable background information on assays for comparative

5 evaluation of the compounds, formulation and administration of rapalogs for treating fungal infection can be found in Holt et al, US Patent No. 6,258,823 (issued July 10, 2001) and references cited therein. Note that antifungal rapalogs of this invention may retain the methoxyl substituent at C7 or may contain any of a variety of replacement substituents, including H and bulky or non-bulky substituents. US Patent No. 6,258,823, for instance,
10 discloses a series of C7 replacement substituents which may be incorporated into the design of compounds of Figure I, especially for antifungal or multimerizing applications.

Compounds of this invention may also be used to treat primary and/or metastatic cancers. They should be useful for reducing tumor size, inhibiting tumor growth or metastasis; treating pain associated with bone cancers; and treating and/or prolonging the
15 survival time of animals or patients with those diseases.

Accordingly this invention provides compounds for use in medical therapy, in particular for use as antifungal, anticancer, immunosuppressive or anti-restenotic agents, or as agents against the other diseases and conditions disclosed herein.

The invention further provides a method of treating a human or non-human animal
20 suffering from any of those diseases or conditions by the administration of an effective amount of the rapalog, and further provides pharmaceutical compositions comprising a compound of the invention together with a pharmaceutically acceptable diluent or carrier, as well as medical devices, such as drug-bearing stents, containing a compound of this invention.

Compounds of this invention may be formulated as disclosed below and elsewhere
25 herein (or using formulations based on those reported for rapamycin or rapamycin derivatives such as AP23573, CCI-779 or RAD001), and may then be administered in treatment effective amounts to patients in need thereof for the treatment of a variety of diseases as noted herein. Such compositions may be administered in any manner useful in directing the
30 active compounds to the recipient's bloodstream or site of action, including orally, parenterally (including intravenous, intraperitoneal and subcutaneous injections as well as injection into joints or other tissues), via stents or other implants, rectally, intranasally, vaginally, and transdermally. For the purposes of this disclosure, transdermal administrations are understood to include all administrations across the surface of the body and the inner
35 linings of bodily passages including epithelial and mucosal tissues. Such administration may be carried out using the present compounds, or pharmaceutically acceptable salts or prodrugs thereof, in lotions, creams, foams, patches, suspensions, solutions, and suppositories (rectal and vaginal).

For parenteral or intraperitoneal administration, solutions or suspensions of these
40 active compounds or a pharmacologically acceptable salt thereof can be prepared in water suitably mixed with a surfactant such as hydroxy-propylcellulose or by adaptation of formulations used for rapamycin, AP23573, CCI779 or RAD001. Dispersions can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof in oils. Under ordinary

5 conditions of storage and use, these preparations may contain a preservative to prevent the growth of microorganisms.

Compositions which contain a compound of this invention and which are suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the composition to be injected should be sterile and should be sufficiently fluid to permit transfer via syringe. It should be stable under the conditions of manufacture and storage and will preferably be protected from the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils. Parenteral formulations which may be adapted for use with rapalogs of this invention are disclosed in U.S. Pat. Nos. 5,530,006; 5,516,770; and 5,616,588.

Formulation, routes of administration and dosing may be selected from, or based upon, those used for rapamycin and other rapalogs used for the same or analogous indications. For treating tumors, it may be preferred to first determine whether the function of PTEN (or PTEN-mediated processes) is partially or wholly deficient in a patient's tumor, and then to selectively treat the patients with PTEN-deficient tumors (See e.g., Neshat et al, PNAS, above). More generally, a preferred approach may be to determine through genotype analysis and/or in vitro culture and study of biopsied tumor samples, those patients with tumors in which the phosphatidylinositol 3 ("PI3") kinase/Akt-mTOR signaling pathway is particular important to cell growth, and then to selectively treat those patients with rapalog. Non-limiting examples of such cancers involving abnormalities in the PI3 kinase/Akt-mTOR pathway include glioma, lymphoma and tumors of the lung, bladder, ovary, endometrium, prostate or cervix which are associated with abnormal growth factor receptors (e.g. EGFR, PDGFR, IGF-R and IL-2); ovarian tumors which are associated with abnormalities in PI3 kinase; melanoma and tumors of the breast, prostate or endometrium which are associated with abnormalities in PTEN; breast, gastric, ovarian, pancreatic, and prostate cancers associated with abnormalities with Akt; lymphoma, cancers of the breast or bladder and head and neck carcinoma associated with abnormalities in eIF-4E; mantle cell lymphoma; breast cancer and head and neck carcinomas associated with abnormalities in Cyclin D; and familial melanoma and pancreas carcinomas associated with abnormalities in P16.

For all of the indications noted herein, it may be beneficial in some cases to treat the patient with a combination of a compound of this invention and one or more other agents useful for treating the relevant disease. The combination may be administered together or separately (e.g., serially). For instance, a patient being treated with an anti-cancer compound of this invention, may (before, during or after such treatment) also be treated one or more other anti-cancer agents such as cisplatin; an antiestrogen (e.g., raloxifene, droloxifene, idoxifene, nafoxidine, toremifene, TAT-59, levomeioxifene, LY-353381, CP-3361656, MDL-103323, EM-800 and ICI-182,780; see e.g. WO 02/13802 which may be adapted to the

5 present invention); an inhibitor of a kinase such as Src, BCR/Abl, kdr, aurora-2, glycogen
synthase kinase 3 ("GSK-3"), cKit, an epidermal growth factor receptor ("EGF-R"), or platelet
derived growth factor receptor ("PDGF-R") for example, including inhibitors such as Gleevec,
Iressa, CP-358774 (Tarceva), ZD-1839, SU-5416, SU11248, or NSC-649890; an antibody
10 (such as Herceptin) to a receptor or hormone (e.g. VEGF or her2) implicated in a cancer, or a
soluble receptor or other receptor antagonist to such receptor; a proteasome inhibitor such
as Velcade; an IKK inhibitor or other NF-kB inhibitor; or radiation. Each component of the
combination may be administered as it would be if given alone, although in some cases
reduced dosing of one or more components may be possible or beneficial in view of the
combined action of the different drugs.

15 Compounds of this invention can also be administered systemically or locally or on
devices such as stents, as described in PCT/US03030 to prevent reocclusion.

Further discussion of pharmaceutical uses, formulation, dosing, and administration is
provided below.

5 Detailed Description of the Invention

In reading this document, the following information and definitions apply unless otherwise indicated. In addition, unless otherwise indicated, all occurrences of a functional group are independently chosen, as the reader is in some cases reminded by the use of a slash mark or prime to indicate simply that the two occurrences may be the same or different (e.g., R and R'). Numbering of atoms in or relating to chemical structures disclosed in this document is with reference to the numbering system shown in Formula I. Also, the reader is directed to pages 15 - 18 of WO 01/14387 for additional definitions and orienting information which supplement the following.

The term "aliphatic" as used herein includes both saturated and unsaturated (but non-aromatic), straight chain (*i.e.*, unbranched), branched, cyclic, or polycyclic non-aromatic hydrocarbon moieties, which are optionally substituted with one or more functional groups. Unless otherwise specified, alkyl, other aliphatic, alkoxy and acyl groups preferably contain 1 - 8 (*i.e.*, "C1 - C8"), and in many cases 1-6 (*i.e.*, "C1 - C6"), contiguous aliphatic carbon atoms. Illustrative aliphatic groups thus include, for example, methyl, ethyl, n-propyl, isopropyl, cyclopropyl, -CH₂-cyclopropyl, allyl, n-butyl, sec-butyl, isobutyl, tert-butyl, cyclobutyl, -CH₂-cyclobutyl, n-pentyl, sec-pentyl, isopentyl, tert-pentyl, cyclopentyl, -CH₂-cyclopentyl, n-hexyl, sec-hexyl, cyclohexyl, -CH₂-cyclohexyl moieties and the like, which again, may bear one or more substituents.

The term "aliphatic" is thus intended to include alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, and cycloalkynyl moieties.

As used herein, the term "alkyl" includes both straight, branched and cyclic alkyl groups. An analogous convention applies to other generic terms such as "alkenyl", "alkynyl" and the like. Furthermore, as used herein, the language "alkyl", "alkenyl", "alkynyl" and the like encompasses both substituted and unsubstituted groups.

The term "alkyl" refers to groups usually having one to eight, preferably one to six carbon atoms. For example, "alkyl" may refer to methyl, ethyl, n-propyl, isopropyl, cyclopropyl, butyl, isobutyl, sec-butyl, tert-butyl, cyclobutyl, pentyl, isopentyl, tert-pentyl, cyclopentyl, hexyl, isohexyl, cyclohexyl, and the like. Suitable substituted alkyl groups include, but are not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl, 3-fluoropropyl, hydroxymethyl, 2-hydroxyethyl, 3-hydroxypropyl, benzyl, substituted benzyl and the like.

The term "alkenyl" refers to groups usually having two to eight, preferably two to six carbon atoms. For example, "alkenyl" may refer to prop-2-enyl, but-2-enyl, but-3-enyl, 2-methylprop-2-enyl, hex-2-enyl, hex-5-enyl, 2,3-dimethylbut-2-enyl, and the like. The language "alkynyl," which also refers to groups having two to eight, preferably two to six carbons, includes, but is not limited to, prop-2-ynyl, but-2-ynyl, but-3-ynyl, pent-2-ynyl, 3-methylpent-4-ynyl, hex-2-ynyl, hex-5-ynyl, and the like.

The term "cycloalkyl" as used herein refers specifically to groups having three to seven, preferably three to ten carbon atoms. Suitable cycloalkyls include, but are not limited

5 to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and the like, which, as in the case of other aliphatic or heteroaliphatic or heterocyclic moieties, may optionally be substituted.

The term "heteroaliphatic" as used herein refers to aliphatic moieties which contain one or more oxygen, sulfur, nitrogen, phosphorous or silicon atoms, *e.g.*, in place of carbon
10 atoms. Heteroaliphatic moieties may be branched, unbranched or cyclic and include heterocycles such as morpholino, pyrrolidinyl, *etc.*

The term "heterocycle", "heterocyclyl", or "heterocyclic" as used herein refers to non-aromatic ring systems having five to fourteen members, preferably five to ten, in which one or more ring carbons, preferably one to four, are each replaced by a heteroatom such as N, O,
15 or S. Non-limiting examples of heterocyclic rings include 3-1H-benzimidazol-2-one, (1-substituted)-2-oxo-benzimidazol-3-yl, 2-tetrahydrofuranyl, 3-tetrahydrofuranyl, 2-tetrahydrothiophenyl, 3-tetrahydrothiophenyl, 2-morpholinyl, 3-morpholinyl, 4-morpholinyl, 2-thiomorpholinyl, 3-thiomorpholinyl, 4-thiomorpholinyl, 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 1-piperazinyl, 2-piperazinyl, 1-piperidiny, 2-piperidiny, 3-piperidiny, 4-piperidiny, 4-
20 thiazolidinyl, diazolonyl, N-substituted diazolonyl, 1-phthalimidinyl, benzoxanyl, benzopyrrolidinyl, benzopiperidinyl, benzoxolanyl, benzothiolanyl, and benzothianyl. Also included within the scope of the term "heterocyclyl" or "heterocyclic", as it is used herein, is a group in which a non-aromatic heteroatom-containing ring is fused to one or more aromatic or non-aromatic rings, such as in an indolinyl, chromanyl, phenanthridinyl, or
25 tetrahydroquinolinyl, where the radical or point of attachment is on the non-aromatic heteroatom-containing ring. The term "heterocycle", "heterocyclyl", or "heterocyclic" whether saturated or partially unsaturated, also refers to rings that are optionally substituted.

The term "aryl" used alone or as part of a larger moiety as in "aralkyl", "aralkoxy", or "aryloxyalkyl", refers to aromatic ring groups having five to fourteen members, such as
30 phenyl, 1-naphthyl, 2-naphthyl, 1-anthracyl and 2-anthracyl. The term "aryl" also refers to rings that are optionally substituted. The term "aryl" may be used interchangeably with the term "aryl ring". "Aryl" also includes fused polycyclic aromatic ring systems in which an aromatic ring is fused to one or more rings. Non-limiting examples of useful aryl ring groups include phenyl, halophenyl, alkoxyphenyl, dialkoxyphenyl, trialkoxyphenyl,
35 alkylendioxyphenyl, naphthyl, phenanthryl, anthryl, phenanthro and the like, as well as 1-naphthyl, 2-naphthyl, 1-anthracyl and 2-anthracyl. Also included within the scope of the term "aryl", as it is used herein, is a group in which an aromatic ring is fused to one or more non-aromatic rings, such as in a indanyl, phenanthridinyl, or tetrahydronaphthyl, where the radical or point of attachment is on the aromatic ring.

40 The term "heteroaryl" as used herein refers to stable heterocyclic, and polyheterocyclic aromatic moieties having 3 – 14, usually 5 – 14, carbon atoms, which moieties may be substituted or unsubstituted and may comprise one or more rings. Substituents include any of the previously mentioned substituents.. Examples of typical heteroaryl rings include 5-membered monocyclic ring groups such as thienyl, pyrrolyl,

5 imidazolyl, pyrazolyl, furyl, isothiazolyl, furazanyl, isoxazolyl, thiazolyl and the like; 6-
 membered monocyclic groups such as pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl and
 the like; and polycyclic heterocyclic ring groups such as benzo[b]thienyl, naphtho[2,3-
 b]thienyl, thianthrenyl, isobenzofuranyl, chromenyl, xanthenyl, phenoxathienyl, indoliziny,
 isoindolyl, indolyl, indazolyl, purinyl, isoquinolyl, quinolyl, phthalazinyl, naphthyridinyl,
 10 quinoxaliny, quinazoliny, benzothiazole, benzimidazole, tetrahydroquinoline cinnoliny,
 pteridinyl, carbazolyl, beta-carboliny, phenanthridinyl, acridinyl, perimidinyl, phenanthroliny,
 phenazinyl, isothiazolyl, phenothiazinyl, phenoxazinyl, and the like (see *e.g.* Katritzky,
 Handbook of Heterocyclic Chemistry). Further specific examples of heteroaryl rings include
 2-furanyl, 3-furanyl, N-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, 3-isoxazolyl, 4-
 15 isoxazolyl, 5-isoxazolyl, 2-oxadiazolyl, 5-oxadiazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 1-
 pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 5-pyrimidyl,
 3-pyridazinyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 5-tetrazolyl, 2-triazolyl, 5-triazolyl, 2-thienyl, 3-
 thienyl, carbazolyl, benzimidazolyl, benzothienyl, benzofuranyl, indolyl, quinoliny,
 benzotriazolyl, benzothiazolyl, benzooxazolyl, benzimidazolyl, isoquinoliny, indolyl, isoindolyl,
 20 acridinyl, or benzoisoxazolyl. Heteroaryl groups further include a group in which a
 heteroaromatic ring is fused to one or more aromatic or nonaromatic rings where the radical
 or point of attachment is on the heteroaromatic ring. Examples include tetrahydroquinoline,
 tetrahydroisoquinoline, and pyrido[3,4-d]pyrimidinyl. The term "heteroaryl" also refers to rings
 that are optionally substituted. The term "heteroaryl" may be used interchangeably with the
 25 term "heteroaryl ring" or the term "heteroaromatic".

An aryl group (including the aryl portion of an aralkyl, aralkoxy, or aryloxyalkyl moiety
 and the like) or heteroaryl group (including the heteroaryl portion of a heteroaralkyl or
 heteroarylalkoxy moiety and the like) may contain one or more substituents. Examples of
 suitable substituents on the unsaturated carbon atom of an aryl or heteroaryl group include
 30 halogen, $-YR^2$ (i.e., including $-R^2$, $-OR^2$, $-SR^2$ and $-NR^2R^5$), $-Y-C(=O)R^2$,
 $-Y-C(=O)OR^2$, $-Y-C(=O)NR^2R^5$, $-Y-C(=NR^2)NR^2R^5$, $-COCOR^2$, $-COMCOR^2$, J, $-CN$,
 $-S(=O)R^2$, $-SO_2R^2$, $-SO_2NR^2R^5$, $-NO_2$, $-NR^5SO_2R^2$ and $-NR^5SO_2NR^2R^5$. To illustrate
 further, substituents in which Y is NR^2 thus include among others, $-NR^2C(=O)R^5$,
 $-NR^2C(=O)NR^5$, $-NR^2C(=O)OR^5$, and $-NR^2C(=NH)NR^5$. Note that R^2 and R^5 substituents
 35 may themselves be substituted or unsubstituted (*e.g.* non-limiting illustrations of an R^5
 moiety include $-alkylhalo$ such as chloromethyl or trichloromethyl; $-alkoxyalkyl$ such as
 methoxyethyl-; mono-, di- and tri-alkoxyphenyl; methylenedioxyphenyl or
 ethylenedioxyphenyl; halophenyl; and alkylamino). Additional illustrative examples include
 1,2-methylene-dioxy, 1,2-ethylenedioxy, protected OH (such as acyloxy), phenyl, substituted
 40 phenyl, $-O$ -phenyl, $-O$ -(substituted) phenyl, $-benzyl$, substituted benzyl, $-O$ -phenethyl (i.e.,
 $-OCH_2CH_2C_6H_5$), $-O$ -(substituted)phenethyl, $-C(O)CH_2C(O)R^2$, $-CO_2R^2$, $-C(=O)R^2$ (i.e.,
 acyl in cases in which R^2 is aliphatic, aryl in cases in which R^2 is aryl and heteroaroyl in

5 cases in which R^2 is heteroaryl), $-C(=O)NR^2R^5$, $-OC(=O)NR^2R^5$, $-C(=NH)NR^2R^5$, and $-OC(=NH)NR^2R^5$. Further examples of substituents include amino, alkylamino, dialkylamino, aminocarbonyl, halogen, alkyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkoxy, nitro, cyano, carboxy, alkoxy carbonyl, alkyl carbonyl, hydroxy, haloalkoxy, and haloalkyl groups.

10 An aliphatic, heteroaliphatic or non-aromatic heterocyclic group may also contain one or more substituents. Examples of suitable substituents on such groups include those listed above for the carbon atoms of an aryl or heteroaryl group and in addition include the following substituents for a saturated carbon atom: $=O$, $=S$, $=NR^2$, $=NNR^2R^5$, $=NNHC(O)R^2$, $=NNHCO_2R^2$, or $=NNHSO_2R^2$. Illustrative examples of substituents on an aliphatic,
15 heteroaliphatic or heterocyclic group include amino, alkylamino, dialkylamino, aminocarbonyl, halogen, alkyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkoxy, nitro, cyano, carboxy, alkoxy carbonyl, alkyl carbonyl, hydroxy, haloalkoxy, or haloalkyl groups.

Illustrative substituents on the nitrogen of an aromatic or non-aromatic heterocyclic
20 ring include $-R^2$, $-NR^2R^5$, $-C(=O)R^2$, $-C(=O)OR^2$, $-C(=O)NR^2R^5$, $-C(=NR^{2'})NR^2R^5$, $-COCOR^2$, $-COMCOR^2$, $-CN$, $-NR^5SO_2R^2$ and $-NR^5SO_2NR^2R^5$.

Examples of substituents on the aliphatic group or the phenyl ring include amino, alkylamino, dialkylamino, aminocarbonyl, halogen, alkyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkoxy, nitro, cyano,
25 carboxy, alkoxy carbonyl, alkyl carbonyl, hydroxy, haloalkoxy, or haloalkyl.

A combination of substituents or variables is permissible only if such a combination results in a stable or chemically feasible compound. For the purposes of this document, a stable compound or chemically feasible compound is one that is not substantially altered when kept at a temperature of 40°C . or less, in the absence of moisture or other chemically
30 reactive conditions, for at least a week.

Certain compounds of this invention may exist in tautomeric forms, and this invention includes all such tautomeric forms of those compounds unless otherwise specified.

Unless a particular stereochemistry is specified verbally or graphically, structures depicted herein are also meant to include all stereochemical forms of the structure; i.e., the R
35 and S configurations for each asymmetric center. Therefore, single stereochemical isomers as well as enantiomeric and diastereomeric mixtures of the present compounds are within the scope of the invention. Thus, this invention encompasses each diastereomer or enantiomer substantially free of other isomers (>90%, and preferably >95%, free from other stereoisomers on a molar basis) as well as a mixture of such isomers. (In chemical structures
40 in this document, a simple line, e.g. the line in Formula I to the substituents at positions 43 and 28, indicates either R or S orientation.) A reference to an "altered" stereochemistry indicates a stereochemistry other than that found at the corresponding site in rapamycin itself.

5 Unless otherwise stated, structures depicted herein are also meant to include compounds which differ only in the presence of an alternative isotope for one or more atoms. For example, compounds having the present structures except for the replacement of a hydrogen by a deuterium or tritium, or the replacement of one or more ^{12}C atoms by a ^{13}C or ^{14}C atom are within the scope of this invention.

10 A JQA-containing rapalog as described herein (i.e., 43-JQA-C(O)O-containing rapalogs) may differ from the corresponding 43-JQA-containing derivative of rapamycin with respect to zero, one, two, three, four, five, six or seven (or more) substituent moieties or functional groups at positions other than position 43. One class of rapalogs of this invention
15 includes JQA-containing rapalogs with no other modifications, relative to rapamycin, i.e., other than the JQA modification at position 43. Another class includes among others JQA-containing rapalogs with additional modification(s) at any one, two, three, four, five or all six of positions C7, C13, C14, C24, C28 and C30. Modifications in rapalog structure are known
20 for a number of previously known rapalogs (see e.g. WO 99/36553, Table III and Liberles et al, 1997, *Proc Natl Acad Sci USA* 94:7825-7830 and *infra*) and may be readily adapted to the present invention. See also WO 01/14387, including among others pages 24 - 30, for information on known modifications and combinations of modifications known for rapamycin which may be used in the design of JQA-containing rapalogs.

25 One subset of JQA-containing rapalogs of special interest for practicing the methods of this invention are those those (or pharmaceutically acceptable derivatives thereof) in which $\text{RC}7\text{a}$ is a moiety other than OMe. This subset ("JQA-containing C7 rapalogs") includes compounds in which one of $\text{R}7\text{a}$ and $\text{R}7\text{b}$ is H and the other is selected from $-\text{R}^{\text{A}}$, $-\text{Z}-\text{R}^{\text{A}}$, $-\text{Z}-(\text{CO})\text{R}^{\text{A}}$, $-\text{Z}-(\text{CO})\text{ZR}^{\text{A}}$, $-\text{NRASO}_2\text{R}^{\text{A}}$ and $-\text{NSO}_2\text{R}^{\text{A}}$, where each Z is independently O, S or NR^{A} . Illustrating this subset are the JQA-containing rapalogs bearing a C7 substituent
30 selected from the following group: aryl; heteroaryl; aryl, heteroaryl or benzyl ether; and $-\text{NH}(\text{CO})\text{OR}^{\text{A}}$, $-\text{NH}(\text{CO})\text{R}^{\text{A}}$, $-\text{NH}(\text{SO}_2)\text{R}^{\text{A}}$ or $-\text{NH}(\text{SO}_2)\text{NHR}^{\text{A}}$ (where R^{A} is a substituted or unsubstituted lower alkyl, e.g., methyl, ethyl, *i*Pr, butyl, benzyl, etc. or is a substituted or unsubstituted phenyl (e.g., *p*-tolyl); In certain embodiments of this subset, $\text{R}7\text{a}$ and $\text{R}7\text{b}$ are independently selected from the following groups: H; a substituted or unsubstituted two
35 to eight carbon straightchain, branched or cyclic alkenyl, alkoxyl or alkylmercapto; and a substituted or unsubstituted aryl, heteroaryl, aryloxy or heteroaryloxy, arylmercapto or heteroarylmercapto. Compounds of this subset include among others those in which $\text{R}7\text{a}$ is H; (together with $\text{R}7\text{b}$) =O; alkoxy; alkylmercapto; amino (primary, secondary, tertiary or quaternary); amido; carbamate; aryl or substituted aryl; phenyl or substituted phenyl;
40 substituted or unsubstituted heteroaryl such as substituted or unsubstituted thiophenyl, furyl, indolyl, etc.; or benzyloxy or substituted benzyloxy. Other illustrative JQA-containing C7 rapalogs which may be used in practicing the methods of this invention include those in

5 which one of R^{7a} and R^{7b} is H and the other is selected from -OEt, -O-propyl, -O-butyl, -
OCH₂CH₂-OH, -O-benzyl, -O-substituted benzyl (including *e.g.*, 3-nitro-, 4-chloro-, 3-iodo-4-
dialkoxy-, 3,4-dimethoxy-, and 2-methoxy-), -S-Me, -S-phenyl, -O(CO)Me, -allyl, -CH₂C(Me)=CH₂,
-OCH₂-CCH, -OCH₂-CC-Me, -OCH₂-CC-Et, -OCH₂-CC-CH₂OH, or -2,4-dimethoxyphenyl,
2,4,6-trimethoxyphenyl, furanyl, thiophen-yl, methylthiophen-yl, pyrrolyl and indolyl. C7-
10 modified JQA-containing rapalogs of particular interest are those bearing a substituted or
unsubstituted aromatic ether, a substituted or unsubstituted benzyl ether or a carbamate
moiety at C7. In C7-modified embodiments, the substituent at C43 may be present in either
stereochemical orientation (or as a mixture of isomers). JQA-containing C7 rapalogs may
15 further vary from the corresponding C7-modified rapamycin at one, two, three, four, five or
more other positions as well.

43 JQA-rapamycin and JQA-containing C7 rapalogs of are of particular interest.

Another subset of JQA-containing rapalogs of special interest in the practice of the
various methods of the invention are those in which the substituents at C24 and C30 are
both other than (=O). Of special interest are those C30 and C24 substituents disclosed in
20 WO 99/36553. This subset includes among others all 43-JQA-containing rapalogs in which
RC₃₀ and RC₂₄ are OH and one of RC_{7a} and RC_{7b} comprises any of the replacement
substituents at that position specified herein, including any of the C7 substituents identified
in WO 01/14387. Of special interest are compounds in which one of RC_{7a} and RC_{7b} is
cyclic aliphatic, aryl, heterocyclic or heteroaryl, which may be optionally substituted. Other
25 compounds within this subset include those in which one, two, three, four or five of the
hydroxyl groups is epimerized, fluorinated, alkylated, acylated or otherwise modified via other
ester, carbamate, carbonate or urea formation. An illustrative compound for example is the
JQA-containing rapalog in which the hydroxyl groups at C28 and C30 are alkylated,
acylated or linked via carbonate formation.

30 Another subset of JQA-containing rapalogs of special interest are the mono- and
difluoro-JQA-containing rapalogs which contain an F at one or both of C13 and C28, as
disclosed in WO 99/36553, with or without additional changes elsewhere in the
JQA-containing rapalog molecule.

Another subset of JQA-containing rapalogs of interest have an RC₂₄ which is other
35 than =O, again, with or without one or more other modifications at other positions relative to
rapamycin.

Other JQA-containing rapalogs of interest include those in which RC₁₄ is OH.

Furthermore, this invention encompasses JQA-containing rapalogs in which one or
more of the carbon-carbon double bonds at the 1,2, 3,4 or 5,6 positions in rapamycin are
40 saturated, alone or in combination with a modification elsewhere in the molecule, *e.g.* at one
or more of C7, C13, C24 C28 and/or C30. It should also be appreciated that the C3,C4

5 double bond may be epoxidized; that the C6 methyl group may be replaced with -CH₂OH or -CH₂OMe; that the C42 methoxy moiety may be demethylated, in any of the compounds disclosed herein, using methods known in the art.

Additional guidance on techniques for preparation and use

10 The production of rapamycin by fermentation and by total synthesis is known. The production of a number of rapalogs as fermentation products is also known. These include among others rapalogs bearing alternative moieties in place of the characteristic cyclohexyl ring or piperolate ring of rapamycin, as well as C7-desmethyl-rapamycin, C29-desmethyl-rapamycin and C29-desmethoxyrapamycin, among others.

15 Methods and materials for effecting various chemical transformations of rapamycin and structurally related macrolides are known in the art. Many such chemical transformations of rapamycin and various rapalogs are disclosed in the patent documents identified in Table I of WO/014387 which help illustrate the level of skill and knowledge in the art of chemical synthesis and product recovery, purification and formulation which may be applied in
20 practicing the subject invention. Also see, e.g., the following patent documents for additional synthetic background:

US4316885	<i>Acyl derivatives of rapamycin</i>
US5023262	<i>Hydrogenated rapamycin derivatives</i>
US5023263	<i>42-oxorapamycin</i>
US5023264	<i>Rapamycin oximes</i>
US5100883	<i>Fluorinated esters of rapamycin</i>
US5102876	<i>Reduction products of rapamycin</i>
US5118677	<i>Amide esters of rapamycin</i>
US5118678	<i>Carbamates of rapamycin</i>
US5120726	<i>Rapamycin hydrazones</i>
US5130307	<i>Aminoesters of rapamycin</i>
US5162333	<i>Aminodiester of rapamycin</i>
US5221670	<i>Rapamycin esters</i>
US5233036	<i>Rapamycin alkoxyesters</i>
US5378696	<i>Rapamycin esters</i>
US5776943	<i>Rapamycin metabolites</i>
WO9205179A1	<i>Carboxylic Acid Esters Of Rapamycin</i>
WO9305046A1	<i>Aminodiester Of Rapamycin</i>

A wide variety of bisphosphonates (alendronate, pamidronate, etc.) are known and are commercially available or readily synthesized which may be used in the practice of this
25 invention, i.e., which may be coupled to rapamycin or a rapalog to produce some of the compounds of this invention. Likewise, a variety of (HO)₂P(=O)CH₂P(=O)(OH)-containing compounds are known and readily synthesized (see e.g., WO 01/44259) for coupling to rapamycin or a rapalog to produce other of the compounds of this invention. Methods and materials for activating, protecting/deprotecting and coupling the starting materials are also
30 well known and are illustrated in the examples which follow.

5 See also PCT/US03/03030 and USSN 10/357,152 for additional guidance on
synthesis, physicochemical characterization, biological characterization and use of other
rapalogs. A variety of biochemical and cell-based methods are known in the art for
characterizing biological activity of these compounds, e.g., measuring binding affinity to
FKBP (see e.g., Sierkierka et al, 1989, Nature 341, 755-757; WO 99/36553 and WO
10 96/41865), inhibition of cell proliferation, etc. One may also measure the effect of these
compounds on any of the pharmacodynamic markers of mTOR inhibitory activity, a variety of
which are known in the art, as well as the effect of these compounds on inhibition of bone
resorption in an animal model of osteoporosis, including for example, an ovariectomized
rodent model. Compounds of this invention, especially those in which one or more hydroxyl
15 groups of the phosphonate and/or phosphinate moieties are not further derivatized, may
also be characterized using conventional materials and methods to assess their binding
affinity for hydroxyapatite to provide an indication of a compound's affinity for bone. For
prodrugs and other derivatives of phosphonates, phosphinates and related moieties, see
Atack et al, J of Pharmacology and Experimental Therapeutics 1994, 270, 70; Arimilli et al,
20 Antiviral Chem & Chemotherapy 1997, 8, 557; Serafinowska et al, J Med Chem, 1995, 35,
1372; Ahlmark, J Med Chem, 1999, 42, 1473; Meier et al, J Med Chem, 1998, 41, 1417;
Krise et al, Advanced Drug Delivery Reviews 1996, 19, 287 and references cited therein, as
well as WO 01/44259

25 **Applications**

In addition to applications and drug combinations noted in PCT/US03/03030 and
USSN 10/357,152 and references cited therein, certain compounds of the invention will be
of interest for their use in treating bone cancers and for their ability to inhibit osteoclast
function, and may be useful in treating patients with debilitating bone disorders such as
30 osteoporosis, particularly osteoporosis associated with the peri and post menopausal
conditions. A compound of this invention may also be administered to patients who have, or
are at risk of, Paget's disease, hypercalcemia associated with bone neoplasms and other
types of osteoporotic diseases and related disorders, including but not limited to involu-
tional osteoporosis, Type I or postmenopausal osteoporosis, Type II or senile osteoporosis,
35 juvenile osteoporosis, idiopathic osteoporosis, endocrine abnormality, hyperthyroidism,
hypogonadism, ovarian agenesis or Turner's syndrome, hyperadrenocorticism or Cushing's
syndrome, hyperparathyroidism, bone marrow abnormalities, multiple myeloma and related
disorders, systemic mastocytosis, disseminated carcinoma, Gaucher's disease, connective
tissue abnormalities, osteogenesis imperfecta, homocystinuria, Ehlers-Danlos syndrome,
40 Marfan's syndrome, Menke's syndrome, immobilization or weightlessness, Sudeck's atrophy,
chronic obstructive pulmonary disease, chronic heparin administration, and chronic ingestion
of anticonvulsant drugs.

Several of these uses are further discussed below.

5

Pharmaceutical uses

Compounds of this invention are of interest as antineoplastic agents, especially for treatment of bone cancers. In particular, the compounds of this invention may be used alone or in combination with other drugs and/or radiation therapy in treating or inhibiting the growth of such cancers. Their use is analogous to that of rapamycin or CCI779 as disclosed in Sorbera et al, "CCI-779" Drugs of the Future 2002, 27(1):7-13; WO 02/4000 and WO 02/13802, for example. Examples of other drugs that can be used to treat cancer patients in conjunction with (i.e., before, during or after administration of a compound of this invention) a compound of this invention include, among others, Zylprim, alemtuzmab, altretamine, amifostine, nastrozole, antibodies against prostate-specific membrane antigen (such as MLN-591, MLN591RL and MLN2704), arsenic trioxide, Avastin® (or other anti-VEGF antibody), bexarotene, bleomycin, busulfan, capecitabine, carboplatin, Gliadel Wafer, celecoxib, chlorambucil, cisplatin, cisplatin-epinephrine gel, cladribine, cytarabine liposomal, daunorubicin liposomal, daunorubicin, daunomycin, dexrazoxane, docetaxel, doxorubicin, Elliott's B Solution, epirubicin, estramustine, etoposide phosphate, etoposide, VP-16, exemestane, fludarabine, 5-FU, fulvestrant, gemcitabine, gemtuzumab-ozogamicin, goserelin acetate, hydroxyurea, idarubicin, idarubicin, Idamycin, ifosfamide, imatinib mesylate, irinotecan (or other topoisomerase inhibitor, including antibodies such as MLN576 (XR11576)), letrozole, leucovorin, leucovorin levamisole, liposomal daunorubicin, melphalan, L-PAM, mesna, methotrexate, methoxsalen, mitomycin C, mitoxantrone, MLN518 or MLN608 (or other inhibitors of the flt-3 receptor tyrosine kinase, PDGF-R or c-kit), itoxantrone, paclitaxel, Pegademase, pentostatin, porfimer sodium, Rituximab (RITUXAN®), talc, tamoxifen, temozolamide, teniposide, VM-26, topotecan, toremifene, Trastuzumab (Herceptin®, or other anti-Her2 antibody), 2C4 (or other antibody which interferes with HER2-mediated signaling), tretinoin, ATRA, valrubicin, vinorelbine, or pamidronate, zoledronate or another bisphosphonate.

Formulations, Pharmaceutical Compositions, dosage and administration

The rapalogs of this invention can exist in free form or, where appropriate, in salt form. Pharmaceutically acceptable salts of many types of compounds and their preparation are well-known to those of skill in the art. Pharmaceutically acceptable salts include conventional non-toxic salts including the quaternary ammonium salts of formed by such compounds with inorganic or organic acids of bases.

Our compounds may form hydrated species when lyophilized with water, or form solvated species when concentrated in a solution with an appropriate organic solvent.

This invention encompasses pharmaceutical compositions comprising a therapeutically (or prophylactically) effective amount of a compound of the invention, and one or more pharmaceutically acceptable carriers and/or other excipients. Carriers include e.g. saline, buffered saline, dextrose, water, glycerol, ethanol, and combinations thereof,

5 and are discussed in greater detail below. The composition, if desired, can also contain
minor amounts of wetting or emulsifying agents, or pH buffering agents. The composition
can be a liquid solution, suspension, emulsion, tablet, pill, capsule, sustained release
formulation, or powder. The composition can be formulated as a suppository, with traditional
binders and carriers such as triglycerides. Oral formulation can include standard carriers
10 such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium
saccharine, cellulose, magnesium carbonate, *etc.* Formulation may involve mixing,
granulating and compressing or dissolving the ingredients as appropriate to the desired
preparation. In another approach, the composition may be formulated into nanoparticles.

The pharmaceutical carrier employed may be, for example, either a solid or liquid.

15 Illustrative solid carriers include lactose, terra alba, sucrose, talc, gelatin, agar, pectin,
acacia, magnesium stearate, stearic acid and the like. A solid carrier can include one or
more substances which may also act as flavoring agents, lubricants, solubilizers, suspending
agents, fillers, glidants, compression aids, binders or tablet-disintegrating agents; it can also
be an encapsulating material. In powders, the carrier is a finely divided solid which is in
20 admixture with the finely divided active ingredient. In tablets, the active ingredient is mixed
with a carrier having the necessary compression properties in suitable proportions, and
compacted in the shape and size desired. The powders and tablets preferably contain up to
99% of the active ingredient. Suitable solid carriers include, for example, calcium phosphate,
magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose,
25 sodium carboxymethyl cellulose, polyvinylpyrrolidone, low melting waxes and ion exchange
resins.

Illustrative liquid carriers include syrup, peanut oil, olive oil, water, *etc.* Liquid carriers
are used in preparing solutions, suspensions, emulsions, syrups, elixirs and pressurized
compositions. The active ingredient can be dissolved or suspended in a pharmaceutically
30 acceptable liquid carrier such as water, an organic solvent, a mixture of both or
pharmaceutically acceptable oils or fats. The liquid carrier can contain other suitable
pharmaceutical additives such as solubilizers, emulsifiers, buffers, preservatives, sweeteners,
flavoring agents, suspending agents, thickening agents, colors, viscosity regulators,
stabilizers or osmo-regulators. Suitable examples of liquid carriers for oral and parenteral
35 administration include water (partially containing additives as above, e.g. cellulose
derivatives, preferably sodium carboxymethyl cellulose solution), alcohols (including
monohydric alcohols and polyhydric alcohols, e.g. glycols) and their derivatives, and oils (e.g.
fractionated coconut oil and arachis oil). For parenteral administration, the carrier can also
be an oily ester such as ethyl oleate and isopropyl myristate. Sterile liquid carriers are useful
40 in sterile liquid form compositions for parenteral administration. The liquid carrier for
pressurized compositions can be halogenated hydrocarbon or other pharmaceutically
acceptable propellant. Liquid pharmaceutical compositions which are sterile solutions or
suspensions can be administered by, for example, intravenous, intramuscular, intraperitoneal
or subcutaneous injection. Injection may be via a single push or by gradual infusion, e.g. 30

5 minute intravenous infusion. The compound can also be administered orally either in liquid or solid composition form.

The carrier or excipient may include a time delay material, examples of which are well known to the art, such as glyceryl monostearate or glyceryl distearate, and may further include a wax, ethylcellulose, hydroxypropylmethylcellulose, methylmethacrylate and the like. When formulated for oral administration, 0.01% Tween 80 in PHOSAL PG-50 (phospholipid concentrate with 1,2-propylene glycol, A. Nattermann & Cie. GmbH) has been recognized as providing an acceptable oral formulation for other compounds, and may be adapted to formulations for various compounds of this invention.

A wide variety of pharmaceutical forms can thus be employed in administering compounds of this invention. If a solid carrier is used, the preparation can be tableted, placed in a hard gelatin capsule in powder or pellet form or in the form of a troche or lozenge. The amount of solid carrier will vary widely but preferably will be from about 25 mg to about 1 g. If a liquid carrier is used, the preparation will be in the form of a syrup, emulsion, soft gelatin capsule, sterile injectable solution or suspension in an ampule or vial or nonaqueous liquid suspension.

To obtain a stable water soluble dosage form, the compound, or a pharmaceutically acceptable salt thereof, may be dissolved in an aqueous solution of an organic or inorganic acid, such as a 0.3M solution of succinic acid or citric acid. Alternatively, acidic derivatives can be dissolved in suitable basic solutions. If a soluble form is not available, the compound is dissolved in a suitable cosolvent or combinations thereof. Examples of such suitable cosolvents include, but are not limited to, alcohol, propylene glycol, polyethylene glycol 300, polysorbate 80, glycerin, polyoxyethylated fatty acids, fatty alcohols or glycerin hydroxy fatty acids esters and the like in concentrations ranging from 0-60% of the total volume.

Various delivery systems are known and can be used to administer the compound, or the various formulations thereof, including tablets, capsules, injectable solutions, encapsulation in liposomes, microparticles, microcapsules, *etc.* Methods of introduction include but are not limited to dermal, intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, pulmonary, epidural, ocular and (as is usually preferred) oral routes. The compound may be administered by any convenient or otherwise appropriate route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (*e.g.*, oral mucosa, rectal and intestinal mucosa, *etc.*) or via a drug-loaded stent and may be administered together with other biologically active agents. Administration can be systemic or local. For treatment or prophylaxis of nasal, bronchial or pulmonary conditions, preferred routes of administration are oral, nasal or via a bronchial aerosol or nebulizer.

In certain embodiments, it may be desirable to administer the compound locally to an area in need of treatment; this may be achieved by, for example, and not by way of limitation, local infusion during surgery, topical application, by injection, by means of a catheter, by means of a suppository, or by means of a skin patch or stent or other implant,

5 said implant typically being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers.

In a specific embodiment, the composition is formulated using routine methods as a pharmaceutical composition for intravenous administration to human beings. Typically, compositions for intravenous administration are solutions in sterile isotonic aqueous buffer. Where necessary, the composition may also include a solubilizing agent and a local anesthetic to ease pain at the site of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a lyophilized powder or water free concentrate in a hermetically sealed container such as an ampoule or sachette indicating the quantity of active agent. Where the composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the composition is administered by injection, an ampoule of sterile water for injection or saline can be provided so that the ingredients may be mixed prior to administration.

For example, a solution of a rapalog of this invention for injection may contain 0.1 to 10 mg/ml, e.g. 1 –3 mg/ml, of rapalog in a diluant solution containing Phosal 50 PG (phosphatidylcholine, propylene glycol, mono- and di-glycerides, ethanol, soy fatty acids and ascorbyl palmitate) and polysorbate 80, containing 0.5 – 4% ethanol, e.g. 1.5% - 2.5% ethanol. As another example, the diluant may contain 2-8%, e.g. 5 – 6%, each of propylene glycol USP and polysorbate 80 in water for injection. We have found that 5.2% of each works well for some rapalogs. Typically a solution is processed using conventional methods and materials, including e.g. one or more rounds of sterile filtration.

Oral formulations containing a compound of this invention may comprise any conventionally used oral forms, including tablets, capsules, buccal forms, troches, lozenges and oral liquids, suspensions or solutions. Capsules may contain mixtures of the active compound(s) with inert fillers and/or diluents such as the pharmaceutically acceptable starches (e.g. corn, potato or tapioca starch), sugars, artificial sweetening agents, powdered celluloses, such as crystalline and microcrystalline celluloses, flours, gelatins, gums, etc. Useful tablet formulations may be made by conventional compression, wet granulation or dry granulation methods and utilize pharmaceutically acceptable diluents, binding agents, lubricants, disintegrants, surface modifying agents (including surfactants), suspending or stabilizing agents, including, but not limited to, magnesium stearate, stearic acid, talc, sodium lauryl sulfate, microcrystalline cellulose, carboxymethylcellulose calcium, polyvinylpyrrolidone, gelatin, alginic acid, acacia gum, xanthan gum, sodium citrate, complex silicates, calcium carbonate, glycine, dextrin, sucrose, sorbitol, dicalcium phosphate, calcium sulfate, lactose, kaolin, mannitol, sodium chloride, talc, dry starches and powdered sugar. Suitable surface modifying agents include nonionic and anionic surface modifying agents. Representative examples of surface modifying agents include, but are not limited to, poloxamer 188, benzalkonium chloride, calcium stearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, magnesium

5 aluminum silicate, and triethanolamine. Oral formulations herein may utilize standard delay or time release formulations to alter the absorption of the active compound(s). The oral formulation may also consist of administering the active ingredient in water or a fruit juice, containing appropriate solubilizers or emulsifiers as needed. Oral formulations which may be adapted for use with rapalogs of this invention are disclosed in U.S. Pat. Nos. 5,559,121; 10 5,536,729; 5,989,591; 5,985,325; 5,145,684 (nanoparticles); 6,197,781; and WO 98/56358. Tablets containing a rapalog of this invention may contain conventional inactive ingredients including for example sucrose, lactose, polyethylene glycol 8000, calcium sulfate, microcrystalline cellulose, pharmaceutical grade glaze, talc, titanium dioxide, magnesium stearate, povidone, poloxamer 188, polyethylene glycol 20,000, glyceryl monooleate, 15 carnauba wax, and other ingredients. Nanosized compositions for oral administration may also be used. In such cases nanoparticles are formed from compositions containing (on a weight/weight basis) 1-20% rapalog, 70 – 95% inert material such as sucrose, 0.1 to 4% of materials such as polyvinyl pyrrolidone and benzylconium chloride and 0 – 1% surfactant such as Tween. An illustrative such composition contains about 15% rapalog, 81% sucrose, 20 2% polyvinyl pyrrolidone, 2% benzylconium chloride and .1% Tween.

In some cases it may be desirable to administer the compounds directly to the airways in the form of an aerosol.

Administration to an individual of an effective amount of the compound can also be accomplished topically by administering the compound(s) directly to the affected area of the 25 skin of the individual. For this purpose, the compound is administered or applied in a composition including a pharmacologically acceptable topical carrier, such as a gel, an ointment, a lotion, or a cream, which includes, without limitation, such carriers as water, glycerol, alcohol, propylene glycol, fatty alcohols, triglycerides, fatty acid esters, or mineral oils.

30 Other topical carriers include liquid petroleum, isopropyl palmitate, polyethylene glycol, ethanol (95%), polyoxyethylene monolaurate (5%) in water, or sodium lauryl sulfate (5%) in water. Other materials such as anti-oxidants, humectants, viscosity stabilizers, and similar agents may be added as necessary. Percutaneous penetration enhancers such as Azone may also be included.

35 In addition, in certain instances, it is expected that the compound may be disposed within transdermal devices placed upon, in, or under the skin. Such devices include patches, implants, and injections which release the compound into the skin, by either passive or active release mechanisms. For the purposes of this disclosure, transdermal administrations are understood to include all administrations across the surface of the body 40 and the inner linings of bodily passages including epithelial and mucosal tissues. Such administrations may be carried out using the present compounds, or pharmaceutically acceptable salts thereof, in lotions, creams, foams, patches, suspensions, solutions, and suppositories (rectal and vaginal).

5 Transdermal administration may be accomplished through the use of a transdermal patch containing the active compound and a carrier that is inert to the active compound, is non toxic to the skin, and allows delivery of the agent for systemic absorption into the blood stream via the skin. The carrier may take any number of forms such as creams and ointments, pastes, gels, and occlusive devices. The creams and ointments may be viscous
10 liquid or semisolid emulsions of either the oil-in-water or water-in-oil type. Pastes comprised of absorptive powders dispersed in petroleum or hydrophilic petroleum containing the active ingredient may also be suitable. A variety of occlusive devices may be used to release the active ingredient into the blood stream such as a semi-permeable membrane covering a reservoir containing the active ingredient with or without a carrier, or a matrix containing the
15 active ingredient. Other occlusive devices are known in the literature.

Suppository formulations may be made from traditional materials, including cocoa butter, with or without the addition of waxes to alter the suppository's melting point, and glycerin. Water soluble suppository bases, such as polyethylene glycols of various molecular weights, may also be used.

20 Materials and methods for producing the various formulations are known in the art and may be adapted for practicing the subject invention. See *e.g.* US Patent Nos. 5,182,293 and 4,837,311 (tablets, capsules and other oral formulations as well as intravenous formulations) and European Patent Application Publication Nos. 0 649 659 (published April 26, 1995; illustrative formulation for IV administration) and 0 648 494
25 (published April 19, 1995; illustrative formulation for oral administration). See also US Patent Nos. 5,145,684 (nanoparticles) and 5,989,591 (solid dosage forms) and WO 98/56358 as well as Yu, K. et al., *Endocrine-Related Cancer* (2001) 8, 249-258 and Georger et al., *Cancer Res.* (2001) 61 1527-1532.

The effective systemic dose of the compound will typically be in the range of about
30 0.01 to about 100 mg/kgs, preferably about 0.1 to about 10 mg/kg of mammalian body weight, administered in single or multiple doses. Generally, the compound may be administered to patients in need of such treatment in a daily dose range of about 1 to about 2000 mg per patient. Administration may be once or multiple times daily, weekly (or at some other multiple-day interval) or on an intermittent schedule. For example, the compound may
35 be administered one or more times per day on a weekly basis (*e.g.* every Monday) for a period of weeks, *e.g.* 4 – 10 weeks. Alternatively, it may be administered daily for a period of days (*e.g.* 2 – 10 days) followed by a period of days (*e.g.* 1 – 30 days) without administration of the compound, with that cycle repeated a given number of times, *e.g.* 4 – 10 cycles. As an example, an anti-cancer compound of the invention may be administered daily for 5 days,
40 then discontinued for 9 days, then administered daily for another 5 day period, then discontinued for 9 days, and so on, repeating the cycle a total of 4 – 10 times.

The amount of compound which will be effective in the treatment or prevention of a particular disorder or condition will depend in part on well known factors affecting drug dosage, and in the case of gene and cell therapy applications, will also depend on the

5 characteristics of the fusion proteins to be multimerized, the characteristics and location of
the genetically engineered cells, and on the nature of the disorder or condition, which can
be determined by standard clinical techniques. In addition, *in vitro* or *in vivo* assays may
optionally be employed to help identify optimal dosage ranges. Effective doses may be
extrapolated from dose-response curves derived from *in vitro* or animal model test systems.
10 The precise dosage level should be determined by the attending physician or other health
care provider and will depend upon well known factors, including route of administration, and
the age, body weight, sex and general health of the individual; the nature, severity and
clinical stage of the disease; the use (or not) of concomitant therapies; and the nature and
extent of genetic engineering of cells in the patient.

15 When administered for the treatment or inhibition of a particular disease state or
disorder, the effective dosage of the rapalog of this invention may vary depending upon the
particular compound utilized, the mode of administration, the condition, and severity thereof,
of the condition being treated, as well as the various physical factors related to the individual
being treated. In many cases, satisfactory results may be obtained when the rapalog is
20 administered in a daily dosage of from about 0.01 mg/kg-100 mg/kg, preferably between
0.01-25 mg/kg, and more preferably between 0.01-5 mg/kg. The projected daily dosages are
expected to vary with route of administration. Thus, parenteral dosing will often be at levels
of roughly 10% to 20% of oral dosing levels.

When the rapalog is used as part of a combination regimen, dosages of each of the
25 components of the combination are administered during a desired treatment period. The
components of the combination may administered at the same time; either as a unitary
dosage form containing both components, or as separate dosage units; the components of
the combination can also be administered at different times during a treatment period, or one
may be administered as a pretreatment for the other.

30 The invention also provides a pharmaceutical pack or kit comprising one or more
containers containing one or more of the ingredients of the pharmaceutical compositions of
the invention. Optionally associated with such container(s) can be a notice in the form
prescribed by a governmental agency regulating the manufacture, use or sale of
pharmaceutical or biological products, which notice reflects approval by the agency of
35 manufacture, use or sale for human administration. The notice or package insert may contain
instructions for use of a rapalog of this invention, consistent with the disclosure herein.



40 The following examples contain important additional information, exemplification and
guidance which can be adapted to the practice of this invention in its various embodiments
and the equivalents thereof. The examples are offered by way illustration should not be
construed as limiting in any way. Numerous modifications and variations of the present
invention should be apparent to one of skill in the art. Such modifications and variations,

5 including design choices in selecting, preparing, formulating and administering the rapalog of this invention; the choice of stent design, materials and methods and materials for loading the rapalog thereon and for delivery the drug-eluting stent;, etc. are intended to be encompassed by the scope of the invention and of the appended claims.

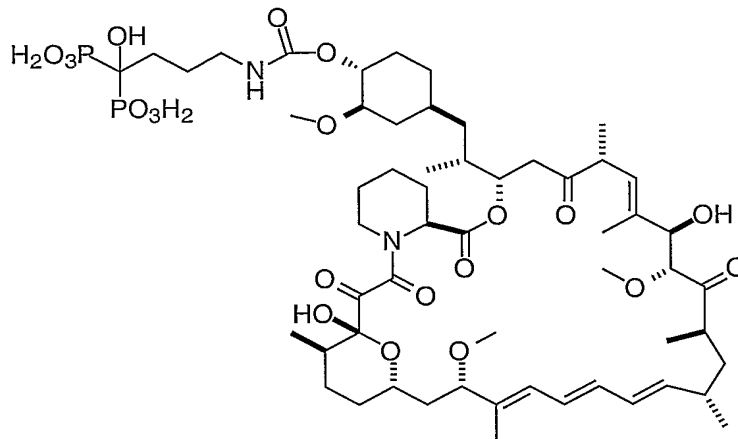
10 Compounds of the invention, as well pharmaceutically acceptable salts, prodrugs or other derivatives thereof, may be prepared by one of ordinary skill in the art of organic chemistry using the guidance provided herein, including the Examples which follow, and the guidance provided by the references cited herein to illuminate the level of skill in the art (especially regarding chemical transformations of rapamycin and its analogs, together with
15 additional methods, materials and background knowledge found in the readily available literature, including works such as, e.g., Reagents for Organic Synthesis, by Fieser and Fieser, John Wiley & Sons, Inc., New York, 2000; Comprehensive Organic Transformations, by Richard C. Larock, VCH Publishers, Inc., New York, 1989; the series Compendium of Organic Synthetic Methods (1989) by Wiley-Interscience; the text Advanced Organic
20 Chemistry, 5th edition, by Jerry March, Wiley-Interscience, New York (2001); or the Handbook of Heterocyclic Chemistry, by Alan R. Katritzky, Pergamon Press Ltd., London, (1985), to name a few. Additionally, the practitioner may find alternative methods useful for preparing our compounds in the chemical literature by searching widely available databases such as, e.g., those available from the Chemical Abstracts Service, Columbus, Ohio, or MDL
25 Information Systems GmbH (previously Beilstein Information Systems GmbH), Frankfurt, Germany.

Preparations of these compounds may use starting materials, reagents, solvents and catalysts that are available from commercial sources or that may be readily prepared by adapting procedures in the references or resources cited above. Commercial sources of
30 starting materials, reagents, solvents, and catalysts useful in preparing invention compounds include, for example, The Aldrich Chemical Company, and other subsidiaries of SigmaAldrich Corporation, St. Louis, Missouri, BACHEM, BACHEM A.G., Switzerland, or Lancaster Synthesis Ltd., United Kingdom.

All of the scientific and patent references cited herein, including the foregoing text
35 books, treatises and series, are hereby expressly incorporated by reference to help clarify the current state of the art.

5

Examples

Example 1: Alendronic acid C-43 rapamycin carbamate*4-Nitrophenyl C-43 rapamycin carbonate*

10 To a cooled (0 °C) solution of rapamycin (5.0 g, 5.47 mmol) in 80 mL of dichloromethane, under an atmosphere of N₂, was added a solution of 4-nitrophenyl chloroformate (1.65 g, 8.20 mmol) in 10 mL DCM, dropwise over ~1 min, followed by a solution of 3,5-lutidine (0.967 g, 9.03 mmol) in 10 mL DCM, dropwise over ~1.5 min (slight exotherms occur following each addition). The reaction solution was stirred at 0 °C for 15 min, then transferred to a

15 separatory funnel containing EtOAc (500 mL) and saturated NaHCO₃ (400 mL). Upon removing the aqueous layer, the organic layer was washed successively with ice cold 1N HCl (1x400 mL), saturated NaHCO₃(2x350 mL), and brine (1x350 mL), then dried over MgSO₄ and concentrated. The crude product was purified by silica gel flash chromatography (eluted with 1% MeOH/DCM) to provide 4.60 g of a yellow solid: 1078 *m/z* (M-H).

20

Alendronic acid C-43 rapamycin carbamate

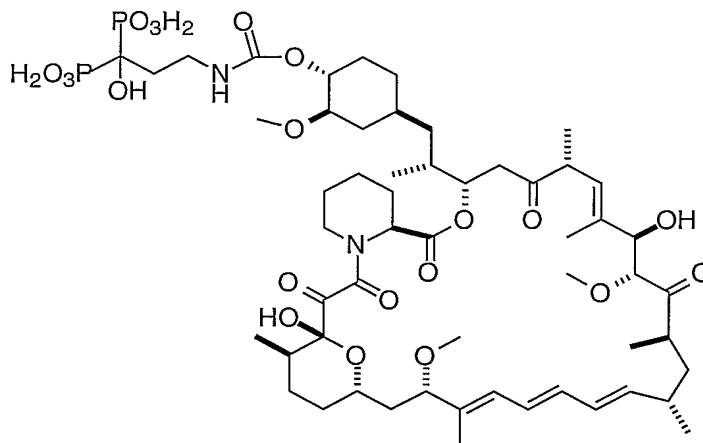
A mixture of alendronic acid (0.346 g, 1.39 mmol) and N,O-bis(trimethylsilyl)acetamide (BSA; 1.41 g, 6.95 mmol) in 4.3 mL of DMSO was heated periodically with a heat gun until all solids dissolved. Stirring at ambient temperature was continued for 1h 15 min (cloudy, pale yellow solution results), upon which a solution of 4-nitrophenyl C-43 rapamycin carbonate (1.0 g, 0.927 mmol) in 10 mL DCM was added followed immediately by a solution of 3,5-lutidine (0.224 g, 2.09 mmol) in 2.8 mL of DCM. The resulting pale yellow reaction solution was stirred at ambient temperature for 18 h (reaction complete by TLC) then concentrated via N₂ flow. The concentrated yellow solution was added 11.5 mL of H₂O resulting in the

25 generation of a sticky solid (solution pH = 2). The solution was decanted off and to the solid was added 25 mL acidic H₂O (pH = 3), resulting in a granular solid that was filtered and washed with acidic H₂O (pH = 3, 1x25 mL). Excess H₂O was removed from the solid in a vacuum desiccator and the resulting off-white solid dissolved in 60 mL DCM, filtered (cotton plug), and the clear filtrate concentrated *in vacuo*. The resulting pale yellow solid was

30

5 washed successively with Et₂O and acidic H₂O (pH = 2), then dissolved in EtOAc and precipitated out of solution with hexanes to provide, following *in vacuo* solvent removal, 0.220 g of a pale yellow solid: ¹H NMR (300 MHz, CDCl₃) δ 4.98 (m, 1H), 4.94 (m, 1H), 4.37 (m, 1H), 2.92 (m, 2H); ³¹P NMR (121 MHz, CDCl₃) δ 25.5; 1188 *m/z* (M-H).

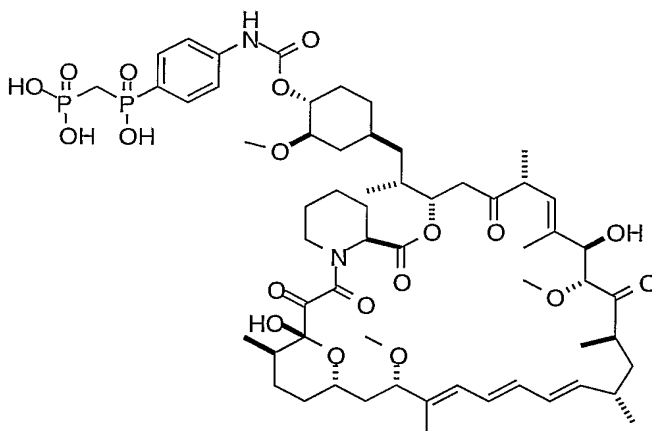
10 **Example 2: Pamidronic acid C-43 rapamycin carbamate**



The title compound was synthesized in a manner similar to that described for Example 1. The product was obtained as a pale yellow solid: ³¹P NMR (121 MHz, CDCl₃) δ 24.9; 1174 *m/z* (M-H).

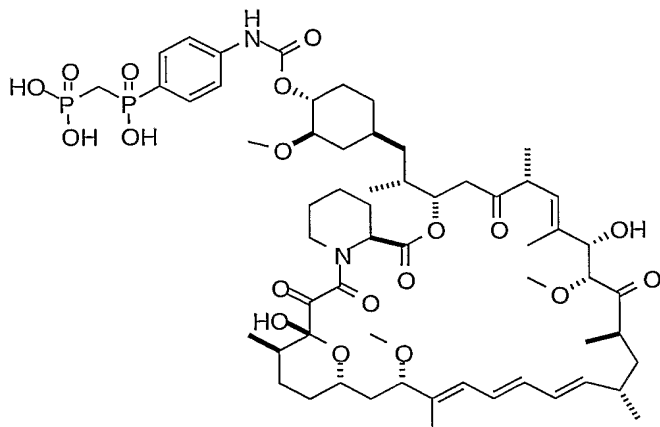
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Example 3: Phenyl-4-phosphinoylmethyl-phosphonic acid C-43 rapamycin carbamate



The title compound was synthesized in a manner similar to that described for Example 1, using [(4-Amino-phenyl)-phosphinoylmethyl]-phosphonic acid. The product was obtained as an off-white solid: ³¹P NMR (121 MHz, CDCl₃) δ 32.3, 20.3; 1190 *m/z* (M-H).

20

5 **Ex 4: Phenyl-4-phosphinoylmethyl-phosphonic acid C-43 28-epi-rapamycin carbamate**

The title compound was synthesized in a manner similar to that described for Example 1, using [(4-Amino-phenyl)-phosphinoylmethyl]-phosphonic acid and 28-epi-rapamycin. The product was obtained as an off-white solid: ^{31}P NMR (121 MHz, CDCl_3) δ 32.4, 20.4; 1208 m/z (M-H+H₂O).

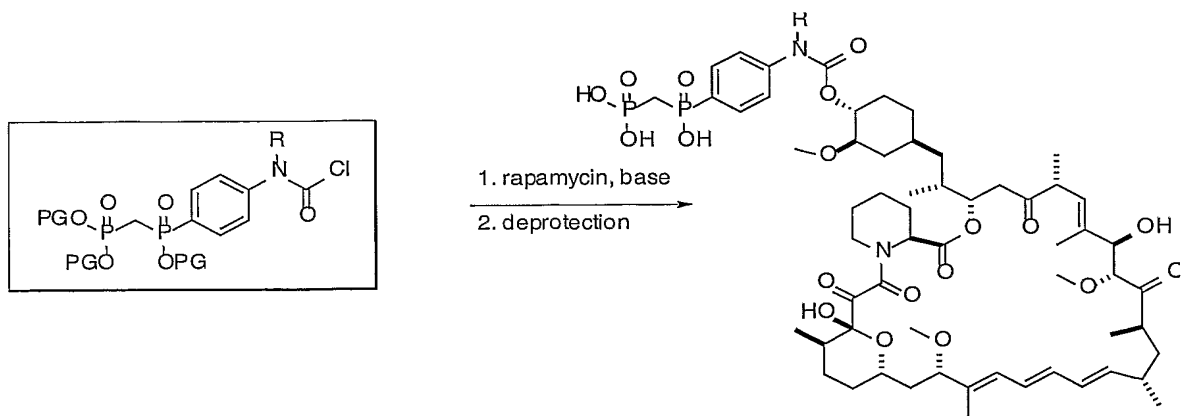
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Example 5: Other carbonates and carbamates of this invention may be synthesized in a manner analogous to that described for Example 1 using an activated C-43 carbonate of rapamycin (or the desired rapalog) and the desired alcohol or amine, appropriately substituted with the desired phosphonate and/or phosphinate groups, and with one or more

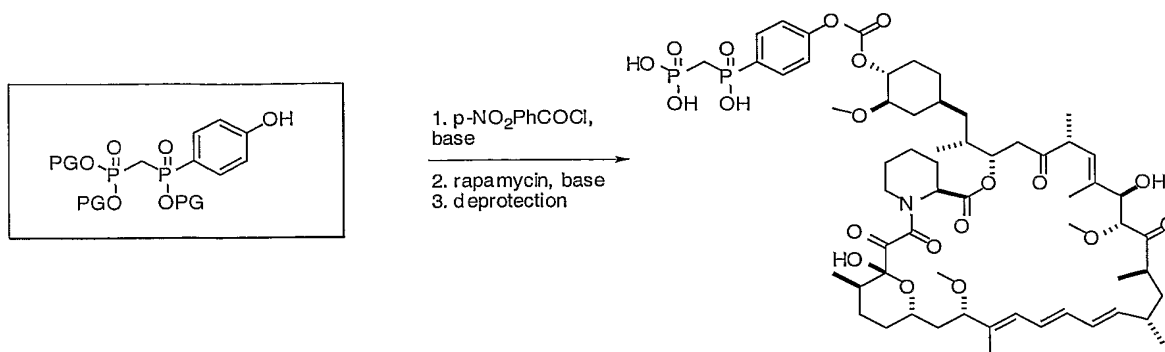
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Alternative synthetic approaches include the following:

20 For carbamates:

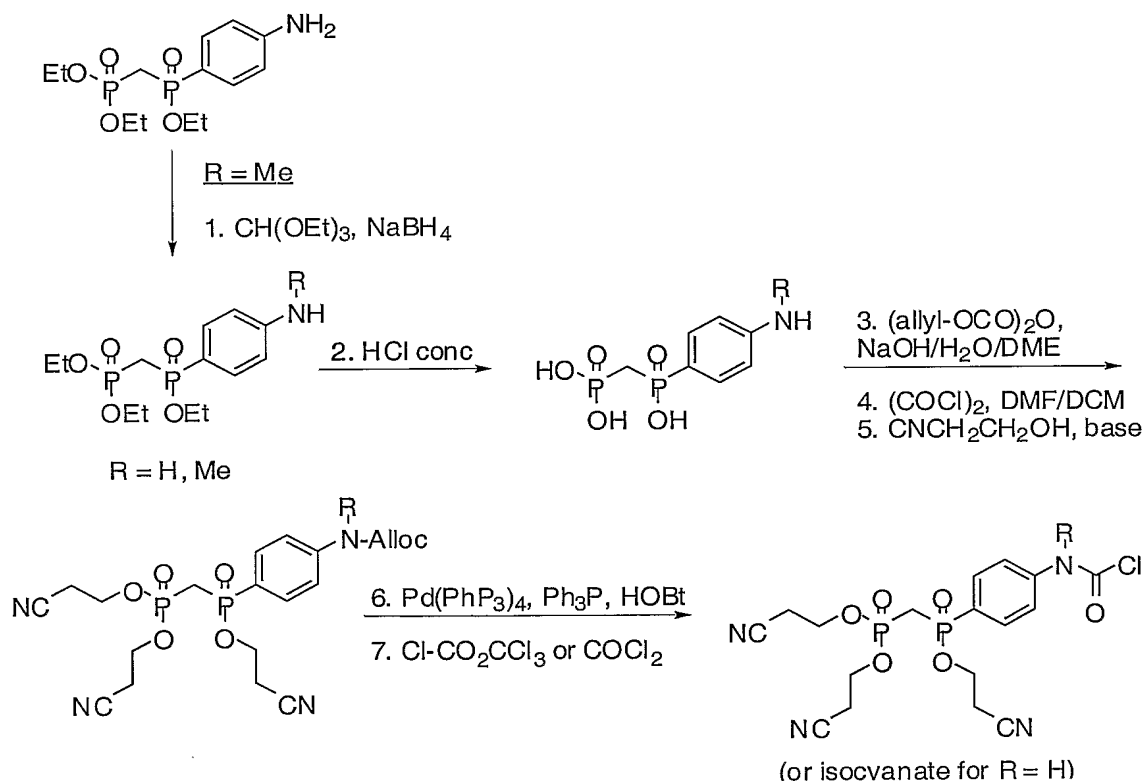


and for carbonates:



- 5 where R = H or alkyl, and PG is a protecting group. Protecting groups that can be removed under particularly mild conditions include trimethyl silyl ("TMS") ethyl-, cyanoethyl, TMS, triethyl silyl, and tri isopropyl silyl, as well as other trisubstituted silyl ethers.

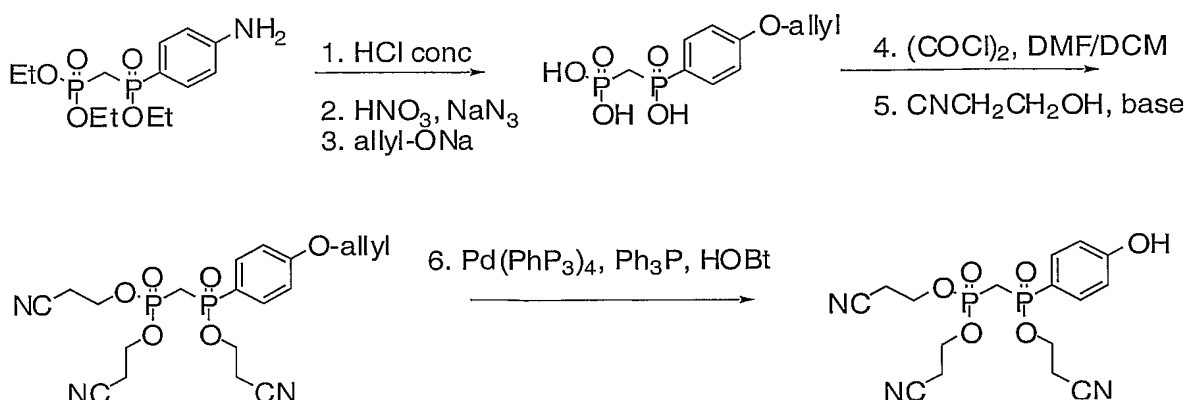
The following synthetic approaches for some intermediates may be of interest to practitioners:



- For Step # 1 see, e.g., Heterocycles (1981), 16(9), 1491-4; for Steps #3 and 6 see, e.g., J. Comb. Chem. (2000), 2(4), 305-13; for Step #7 (R = H), see, e.g., PCT Int. Appl. 8702357, 23 Apr 1987; J. Med. Chem. (1987), 30(7), 1166-76 and J. Med. Chem. (1987), 30(1), 62-7.
15 For Step #7 (R = Me), see, e.g., J. Org. Chem. (1983), 48(24), 4750-6.

- and -

5



For Step # 2 , see e.g., Austr. J. Chem. (1990), 43(6), 997-1007; for Step #3 see e.g., Chem
10 Reviews (1954), 54, 1-57; and for Step #6 see e.g., J. Comb. Chem. (2000), 2(4), 305-13.

EXAMPLE 6. Hydroxyapatite Assay

Hydroxyapatite is the principal mineral component of bone. Hydroxyapatite
15 adsorption chromatography is used as an assay to evaluate the bone-targeting potential of
a compound.

Method: The retention time of a test compound is measured using a linear gradient
from 10 mM sodium phosphate, 0.15 N NaCl, pH = 6.8 to 500 mM sodium phosphate, 0.15 N
20 NaCl, pH = -6.8 on a TSK-Gel HA 1000 high pressure liquid chromatography column (7.5 mm
x 75 mm). The retention time of the compound is expressed in terms of $K = (\text{retention time} - \text{void time}) / \text{void}$. This K value is corrected using two reference compounds to correct from
inter-column and inter-system variation to obtain a K' value.

Reference Compounds: K' values were determined for known bone targeted
25 compounds, the bisphosphonate, alendronate and tetracycline. Alendronate gave a K'
value of 3.7 and tetracycline gave a K' value of 2.0.

EXAMPLE 7. In Vivo Anti-Resorptive Testing in Hypercalcemic Mouse

A mouse hypercalcemia model for determining the efficacy of inhibitors of bone resorption
may be used to compare compounds of this invention. This model exploits the intrinsic
30 effects of PTH (1-34) to stimulate the resorptive activity of osteoclasts in vivo. In one version
of the assay, compounds are injected into mice subcutaneously, once or twice per day for
five consecutive days. On the third day of compound treatments, PTH administration begins.
PTH (20 $\mu\text{g}/\text{kg}$) is given four times per day, subcutaneously, until the end of the study.
Control animals receive PTH but do not receive test compounds. Blood samples are
35 collected from the animals to obtain baseline (pre-PTH treatment), 48 hour and 72 hour (after

5 initiation of PTH treatment) serum samples. The serum samples are analyzed for calcium concentration using the quantitative colorimetric assay reagent Arsenazo III (Sigma). Calcium serum levels for treated groups are compared to calcium serum levels of control groups and a percentage of inhibition of hypercalcemia is calculated for each time point. When a compound is effective in inhibiting the activity of osteoclasts, observed serum
10 calcium concentrations are lower than in animals that receive only PTH in the absence of test compound.

Example 8. Cytotoxicity and Inhibition of Tumor Growth:

Compounds may be assayed for anti-tumor activity using in vivo and in vitro assays
15 which are well known to those skilled in the art. Generally, initial screens of compounds to identify candidates for anti-cancer drugs are performed in cellular in vitro assays. Compounds identified as having anti-cell proliferative activity can then be subsequently assayed in whole organisms for anti-tumor activity and toxicity. The initial screens are preferably cellular assays which can be performed rapidly and cost-effectively relative to
20 assays that use whole organisms. For purposes of the present invention, the term "anti-proliferative compound" is used to mean compounds having the ability to impede or stop cells from progressing through the cell cycle and dividing. For purposes of the present invention, the terms "anti-tumor" and "anti-cancer" activity are used interchangeably.

Methods for determining cell proliferation are well known and can be used to identify
25 compounds with anti-proliferative activity. In general, cell proliferation and cell viability assays are designed to provide a detectable signal when cells are metabolically active. Compounds are tested for anti-cell proliferation activity by assaying for a decrease in metabolic activity. Commonly used methods for determining cell viability depend upon, for example, membrane integrity (e.g. trypan blue exclusion) or incorporation of nucleotides during cell proliferation
30 (e.g. BrdU or 3H-thymidine).

Preferred methods of assaying cell proliferation utilize compounds that are converted into a detectable compound during cell proliferation. Particularly preferred compounds are tetrazolium salts and include without limitation MTT (3-(4, 5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; Sigma-Aldrich, St. Louis, MO), MTS (3-(4,5-dimethylthiazol-2-yl)-
35 5-(3-carboxymethoxyphenyl)- 2-(4-sulfophenyl)-2H-tetrazolium), XTT (2,3-bis(2-Methoxy-4-nitro-5-sulfophenyl)-2H-tetrazolium-5-carboxanilide), INT, NBT, and NTV (Bernas et al. *Biochim Biophys Acta* 1451(1):73-81, 1999). Preferred assays utilizing tetrazolium salts detect cell proliferation by detecting the product of the enzymatic conversion of the tetrazolium salts into blue formazan derivatives, which are readily detected by spectroscopic
40 methods (Mosman. *J. Immunol. Methods.* 65:55-63, 1983).

Generally, preferred methods for assaying cell proliferation involve incubating cells in a desired growth medium with and without the compounds to be tested. Growth conditions for various prokaryotic and eukaryotic cells are well-known to those of ordinary skill in the art (Ausubel et al. *Current Protocols in Molecular Biology.* Wiley and Sons. 1999; Bonifacino et

5 al. Current Protocols in Cell Biology. Wiley and Sons. 1999 both incorporated herein by
reference). To detect cell proliferation, the tetrazolium salts are added to the incubated
cultured cells to allow enzymatic conversion to the detectable product by active cells. Cells
are processed, and the optical density of the cells is determined to measure the amount of
formazan derivatives. Furthermore, commercially available kits, including reagents and
10 protocols, are available for examples, from Promega Corporation (Madison, WI), Sigma-
Aldrich (St. Louis, MO), and Trevigen (Gaithersburg, MD).

Any cultured cell line may be used to screen compounds for antiproliferative activity.
In certain embodiments of the invention cell lines utilized include, but are not limited to,
Exemplary cell lines utilized for the determination of the ability of inventive compounds to
15 inhibit cellular proliferation include, but are not limited to COLO 205 (colon cancer), DLD-1
(colon cancer), HCT-15 (colon cancer), HT29 (colon cancer), HEP G2 (Hepatoma), K-562
(Leukemia), A549 (Lung), NCI -H249 (Lung), MCF7 (Mammary), MDA-MB-231 (Mammary),
SAOS-2 (Osteosarcoma), OVCAR-3 (Ovarian), PANC-1 (Pancreas), DU-145 (Prostate), PC-3
(Prostate), ACHN (Renal), CAKI-1 (Renal), MG-63 (Sarcoma).

20 Preferably, the cell line is a mammalian, but is not limited to mammalian cells since
lower order eukaryotic cells such as yeast may also be used to screen compounds.
Preferred mammalian cell lines are derived from humans, rats, mice, rabbits, monkeys,
hamsters, and guinea pigs since cells lines from these organisms are well-studied and
characterized. However, the present invention does not limit the use of mammalian cells
25 lines to only the ones listed.

Suitable mammalian cell lines are often derived from tumors. For example, the
following tumor cell-types may be sources of cells for culturing cells: melanoma, myeloid
leukemia, carcinomas of the lung, breast, ovaries, colon, kidney, prostate, pancreas and
testes), cardiomyocytes, endothelial cells, epithelial cells, lymphocytes (T-cell and B cell),
30 mast cells, eosinophils, vascular intimal cells, hepatocytes, leukocytes including mononuclear
leukocytes, stem cells such as haemopoetic, neural, skin, lung, kidney, liver and myocyte
stem cells (for use in screening for differentiation and de-differentiation factors), osteoclasts,
chondrocytes and other connective tissue cells, keratinocytes, melanocytes, liver cells,
kidney cells, and adipocytes. Non-limiting examples of mammalian cells lines that have been
35 widely used by researchers include HeLa, NIH/3T3, HT1080, CHO, COS-1, 293T, WI-38 and
CV1/EBNA-1.

Other in vitro cellular assays may be used which rely upon a reporter gene to detect
metabolically active cells. Non-limiting examples of reporter gene expression systems include
green fluorescent protein (GFP), and luciferase. As an example of the use of GFP to screen
40 for potential antitumor drugs, Sandman et al. (Chem Biol. 6:541-51; incorporated herein by
reference) used HeLa cells containing an inducible variant of GFP to detect compounds that
inhibited expression of the GFP, and thus inhibited cell proliferation.

Compounds identified by in vitro cellular assays as having anti-cell proliferation
activity are then tested for anti-tumor activity in whole organisms. Preferably, the organisms

5 are mammalian. Well-characterized mammalian systems for studying cancer include rodents such as rats and mice. Typically, a tumor of interest is transplanted into a mouse having a reduced ability to mount an immune response to the tumor to reduce the likelihood of rejection. Such mice include for example, nude mice (athymic) and SCID (severe combined immunodeficiency) mice. Other transgenic mice such as oncogene containing mice may be
10 used in the present assays (see for example USP 4,736,866 and USP 5,175,383). For a review and discussion on the use of rodent models for antitumor drug testing see Kerbel (Cancer Metastasis Rev. 17:301-304, 1998-99).

In general, the tumors of interest are implanted in a test organism preferably subcutaneously. The organism containing the tumor is treated with doses of candidate anti-
15 tumor compounds. The size of the tumor is periodically measured to determine the effects of the test compound on the tumor. Some tumor types are implanted at sites other than subcutaneous sites (e.g. intraperitoneal sites) and survival is measured as the endpoint. Parameters to be assayed with routine screening include different tumor models, various tumor and drug routes, and dose amounts and schedule. For a review of the use of mice in
20 detecting antitumor compounds see Corbett et al. (Invest New Drugs. 15:207-218, 1997; incorporated herein by reference)

25 **Example 9: Biological activity**

A. Inhibition of proliferation of HT1080 human fibrosarcoma cells; FKBP-binding

Compounds of this invention which were tested for inhibitory activity on the proliferation of
30 HT1080 cells yielded IC₂₅ values of 20 nM, retaining still significant activity of the parent molecule, rapamycin (IC₂₅ = 0.1 nM), and exhibiting far greater potency than that seen with the bisphosphonates Zolendronate and Alendronate on osteosarcoma cells (IC₅₀ values of 7 – 75 μM). One of the compounds was tested for FKBP-binding and was found to have an IC₅₀ of 5 nM in a conventional FKBP-binding assay, only slightly off rapamycin's 1 nM IC₅₀.

35

B. Inhibition of osteoclasts formation (non-bone)

Compounds of this invention which were tested for inhibitory activity on the formation of
40 osteoclasts provided IC₅₀ values of 10 – 100 nM, retaining significant activity of the parent molecule, rapamycin (IC₅₀ = 1 – 10 nM), and exhibiting far greater potency than that seen with Zolendronate and Alendronate (IC₅₀ = 1 – 10 μM).

5 **C. Demonstration of antiresorptive activity in hypercalcemic mice**

Compounds of this invention which were tested for inhibition of PTH-induced hypercalcemia in a 5-day mouse study demonstrated activity as good as or better than rapamycin in initial studies. One of the compounds demonstrated significant and sustained reduction (~70%) of
10 serum calcium levels when dosed at 10 mg/kg (bid, IP). It also demonstrated similar inhibition with a single oral dose of 50 mg/kg (IP).

In a separate experiment in PTH-induced hypercalcemic mice, the compound demonstrated superior reduction (83%, Day 5) of serum calcium levels when dosed at 10 mg/kg (bid, IP) compared to rapamycin dosed similarly (38% inhibition, Day 5).

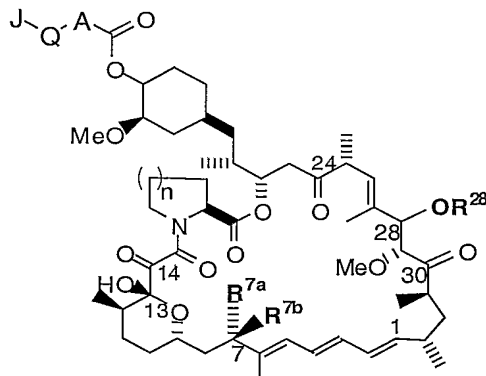
15 In that study, mice were administered test compounds or vehicle twice daily by the intraperitoneal route of administration for five consecutive days. Baseline serum calcium was measured on Day 2. Parathyroid hormone was administered subcutaneously at a dose of 20 µg/kg, four times a day, on Days 3, 4, and 5 to drug treatment and vehicle control
20 groups. Serum calcium levels were measured on Days 4 and 5.

A second compound of this series, also produced per the foregoing examples, was found to have very favorable FKBP-binding activity (IC₅₀ = 3 nM) and demonstrated extremely potent activity in our mouse hypercalcemia assay, with inhibition equal to or greater than equivalent
25 (molar) doses of rapamycin (as low as 0.3 mg/kg, daily IP).

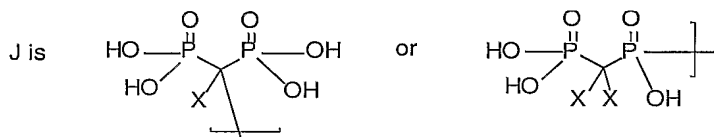
These results demonstrate the achievement of dual *in vitro* antiproliferative and antiresorptive effects with compounds of this invention containing aliphatic and aromatic groups Q. Both types of compounds demonstrated potent and sustained inhibition of PTH-
30 induced hypercalcemia in mice.

5 **Claims:**

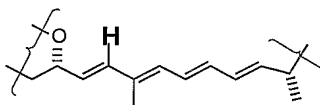
1. A compound of the formula:



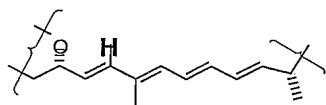
10 wherein each occurrence of **A** is independently -O-, -S- or -NR²-; each occurrence of **Q** is independently an aliphatic, heteroaliphatic, aryl or heteroaryl moiety, linking **A** to **J**;



each occurrence of **X** is independently H, -OR or halo;

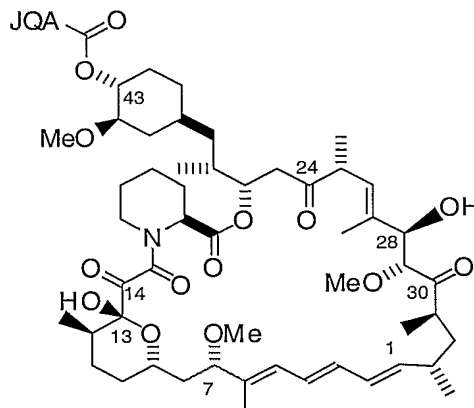


15 one of **R^{7a}** and **R^{7b}** is H and the other is H, halo, -R^A, -OR^A, -SR^A, -OC(O)R^A, -OC(O)NR^AR^B, -NR^AR^B, -NR^BC(O)R^A, -NR^BC(O)OR^A, -NR^BSO₂R^A or -NR^BSO₂NR^AR^B; or **R^{7a}** and **R^{7b}**, taken together, are H in the tetraene moiety:

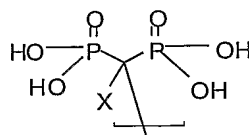


20 R^A is R², R^B is OH or R² and each occurrence of R² is independently H or an aliphatic, heteroaliphatic, aryl, or heteroaryl moiety (in some cases one or both of R^A and R^B is H); **R²⁸** is hydrogen or COAQJ; and **n** is 1 or 2; wherein each of the foregoing aliphatic and heteroaliphatic moieties is independently branched or unbranched, or cyclic or acyclic, and substituted or unsubstituted, and each aryl or heteroaryl moiety is independently substituted or unsubstituted.

5 2. The compound of claim 1 of the formula:

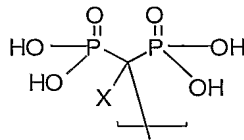


- 3. The compound of claim 1 wherein A is NR².
- 4. The compound of claim 2 wherein A is NR².
- 10 5. The compound of claim 1 wherein A is O.
- 6. The compound of claim 2 wherein A is O.
- 7. The compound of claim 1 wherein Q is a 1 – 8-carbon alkyl moiety.
- 8. The compound of claim 2 wherein Q is a 1 – 8-carbon alkyl moiety.
- 9. The compound of claim 3 wherein Q is a 1 – 8-carbon alkyl moiety.
- 15 10. The compound of claim 4 wherein Q is a 1 – 8-carbon alkyl moiety.
- 11. The compound of claim 5 wherein Q is a 1 – 8-carbon alkyl moiety.
- 12. The compound of claim 6 wherein Q is a 1 – 8-carbon alkyl moiety.
- 13. The compound of claim 1 wherein Q is an aryl or heteroaryl moiety.
- 14. The compound of claim 2 wherein Q is an aryl or heteroaryl moiety.
- 20 15. The compound of claim 3 wherein Q is an aryl or heteroaryl moiety.
- 16. The compound of claim 4 wherein Q is an aryl or heteroaryl moiety.
- 17. The compound of claim 5 wherein Q is an aryl or heteroaryl moiety.
- 18. The compound of claim 6 wherein Q is an aryl or heteroaryl moiety.
- 19. The compound of any of claims 3, 4, 9, 10, 15 or 16 in which –NR²– is
- 25 –NH–.
- 20. The compound of any of claims 3, 4, 9, 10, 15 or 16 in which the R² moiety of –NR²– is a 1 – 8 carbon alkyl group.
- 21. The compound of any of claims 1 – 18 wherein J is:

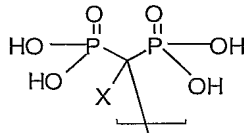


30

5 22. The compound of claim 19 wherein J is:

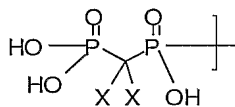


23. The compound of claim 20 wherein J is:

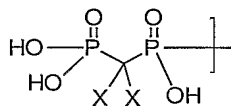


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24. The compound of any of claims 1 – 18 wherein J is:

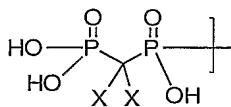


25. The compound of claim 19 wherein J is:



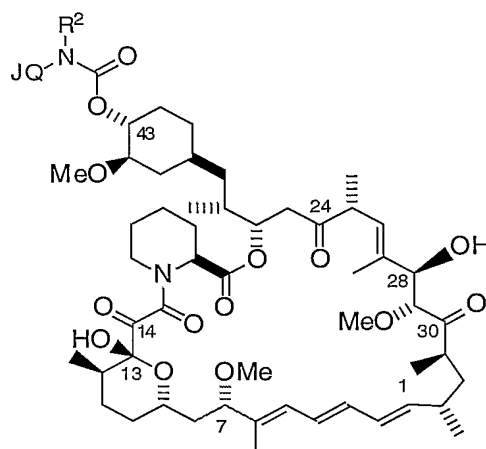
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26. The compound of claim 20 wherein J is:

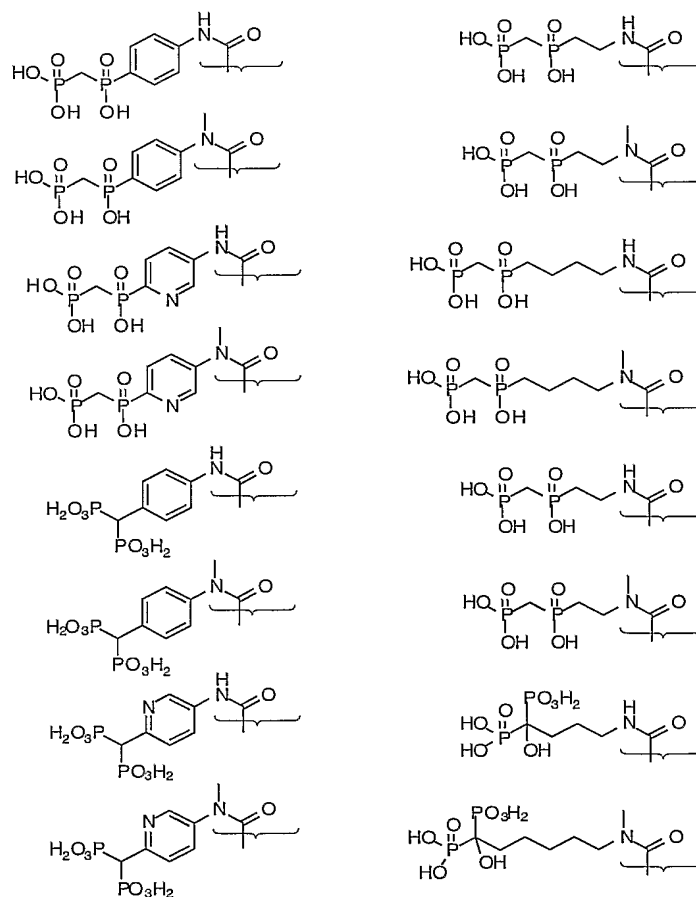


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27. The compound of claim 1 having the structure:



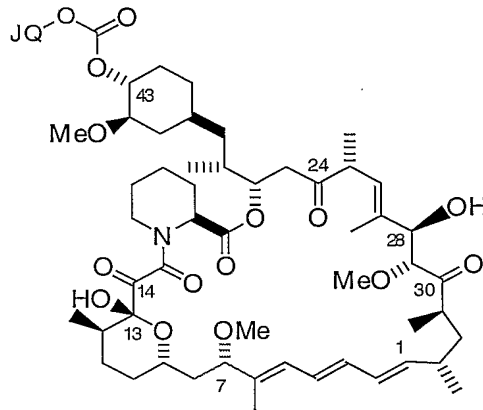
wherein JQA-O-CO- is selected from the following:



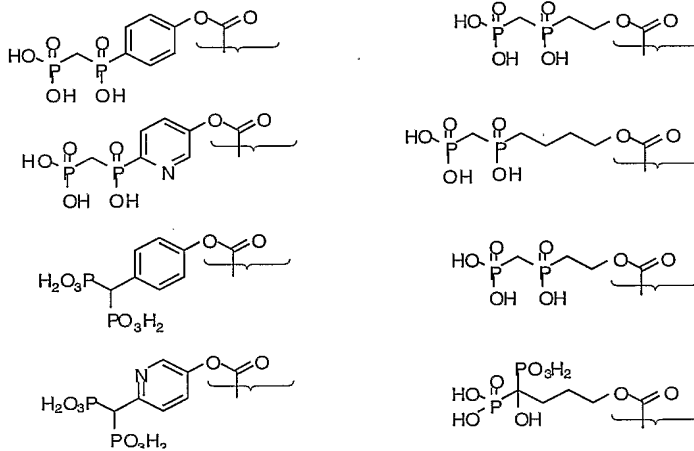
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5

28. The compound of claim 1 having the formula:



wherein JQOCOO- is selected from:



10

29. A composition comprising a compound of any of claims 1 - 28, together with a pharmaceutically acceptable vehicle and optionally containing one or more pharmaceutically acceptable excipients.

15

30. A method for treating cancer by administering to a patient in need thereof a compound of any of claim 1 - 28.

20

31. The use of compound of any of claim 1 - 28 for the preparation of a medicament for the treatment of cancer or a disease involving undue bone resorption.